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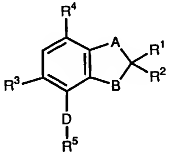
(54) OXYGEN-CONTAINING HETEROCYCLIC COMPOUNDS

(57) An oxygen-containing heterocyclic compound represented by following Formula (I):



(I)

wherein R^1 and R^2 independently represent hydrogen, lower alkyl, cyano, $-(CH_2)_n$-E-CO-F (wherein E represents a bond, O, or NH; F represents OR^6 or NR^7R^8; and n represents an integer of 0 to 4), or the like; R^1 and R^2 are combined to represent a saturated carbon ring together with a carbon atom adjacent thereto; or R^2, and R^{11} or R^{13} described below are combined to form a single bond; R^3 represents hydrogen, phenyl, or halogen; R^4 represents hydroxy, lower alkoxy, or the like; A represents $-C(R^9)(R^{10})-$ or O; B represents O, NR^{11}, $-C(R^{12})(R^{13})-$, or $-C(R^{14})(R^{15})-C(R^{16})(R^{17})-$; D represents (i) $-C(R^{18})(R^{19})-X-$ (wherein X represents $-C(R^{21})(R^{22})-$, S, or NR^{23}), (ii) $-C(R^{19a})=Y-$ [Y represents -

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$C(R^{24})$-Z- (wherein Z represents CONH, $CONHCH_2$, or a bond), or N], or (iii) a bond; and R^5 represents aryl, an aromatic heterocyclic group, cycloalkyl, pyridine-N-oxide, cyano, or lower alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

Description

Technical Field

The present invention relates to oxygen-containing heterocyclic compounds which exhibit phosphodiesterase (PDE) IV inhibitory activity and which are useful as therapeutic agents for inflammatory allergic diseases such as bronchial asthma, allergic rhinitis, and nephritis; autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, Crohn's disease, psoriasis, and systemic lupus erythematosus; diseases of the central nervous system such as depression, amnesia, and dementia; organopathy associated with ischemic reflux caused by cardiac failure, shock, and cerebrovascular diseases, and the like; insulin-resistant diabetes; wounds; AIDS, and the like.

Background Art

Heretofore, it is known that the functions of numerous hormones and neurotransmitters are expressed by an increase in the concentration of adenosine 3',5'-cyclic monophosphate (cAMP) or guanosine 3',5'-cyclic monophosphate (cGMP), both of which are the secondary messengers in cells. The cellular concentrations of cAMP and cGMP are controlled by the generation and decomposition thereof, and their decomposition is carried out by PDE. Therefore, when PDE is inhibited, the concentrations of these secondary cellular messengers increase. Up to the present, 7 kinds of PDE isozymes have been found, and the isozyme-selective PDE inhibitors are expected to exhibit pharmacological effect based on their physiological significance and distribution in vivo (TiPS, 1990, 11, 150, TiPS, 1991, 12, 19).

It is known that the activation of inflammatory leukocytes can be suppressed by increasing the concentration of the cellular cAMP. The activation of leukocytes causes secretion of inflammatory cytokines such as tumor necrosis factor (TNF), and expression of the cellular adhesion molecules such as intercellular adhesion molecules (ICAM), followed by cellular infiltration [J. Mol. Cell. Cardiol., 1989, 12, (Suppl. II), S61].

It is known that the contraction of a respiratory smooth muscle can be suppressed by increasing the concentration of the cellular cAMP (T. J. Torphy in Directions for New Anti-Asthma Drugs, eds S. R. O'Donell and C. G. A. Persson, 1988, 37, Birkhauser-Verlag). The contraction of a respiratory smooth muscle is a main symptom of bronchial asthma. Inflammatory-leukocyte infiltration of neutrophils and the like is observed in lesions of organopathy associated with ischemic reflux such as myocardial ischemia. It has been found that the IV type PDE (PDE IV) mainly participates in the decomposition of cAMP in these inflammatory cells and tracheal smooth muscle cells. Therefore, the inhibitors selective for PDE IV are expected to have therapeutic and/or preventive effect on inflammatory diseases, respiratory obstructive diseases, and ischemic diseases.

Further, the PDE IV inhibitors are expected to prevent the progress and spread of the inflammatory reaction transmitted by inflammatory cytokines such as TNFα and interleukin (IL)-8, because the PDE IV inhibitors suppress the secretion of these cytokines by increasing the concentration of cAMP. For example, TNFα is reported to be a factor of insulin-resistant diabetes because it declines the phosphorylating mechanism of insulin receptors of muscle and fat cells (J. Clin. Invest., 1994, 94, 1543-1549). Similarly, it is suggested that TNFα participates in the onset and progress of autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and Crohn's disease, and that the PDE IV inhibitors are useful for these diseases (Nature Medicine, 1995, 1, 211-214 and 244-248).

Drugs which increase cAMP are reported to enhance the healing of wounds [Nippon Yakuri-gakkai, the 68th annual meeting (Nagoya), P3-116, 1995].

PDE IV-selective inhibitors having catechol structures are disclosed in WO96-00218, WO96-00215, WO95-35285, WO95-35284, WO95-35283, WO95-35281, WO95-28926, WO95-27692, WO95-24381, WO95-22520, WO95-20578, WO95-17399, WO95-17392, WO95-14681, WO95-14680, WO95-14667, WO95-09837, WO95-09836, WO95-09627, WO95-09624, WO95-09623, WO95-08534, WO95-04046, WO95-04045, WO95-03794, WO95-01338, WO95-00516, WO95-00139, US5461056, EP0685479, EP0685475, EP0685474, EP0671389, WO93-25517, WO94-25437, EP0623607, WO94-20446, WO94-20455, WO94-14800, WO94-14742, WO94-12461, WO94-10118, WO94-02465, WO93-19751, WO93-19750, WO93-19749, WO93-19748, WO93-19747, WO93-18024, WO93-15048, WO93-07141, Japanese Published Unexamined Patent Application No. 117239/93, WO92-19594, and EP0497564.

Compounds which have a benzofuran structure and PDE IV-inhibitory activity are reported (Bioorganic Med. Chem. Lett., 1994, 14, 1855-1860, EP-0685479, WO96-03399).

Heretofore, benzofuran derivatives are industrially useful and are disclosed in patents of intermediates of product materials, light emitting elements, agricultural chemicals, anthelminthics, drugs, and the like.

Benzofuran, benzopyran, and benzodioxole derivatives which have a carboxyl group or a tetrazolyl group are disclosed in J. Med. Chem., 1988, 31, 84-91, and Japanese Published Unexamined Patent Application Nos. 50977/86, 126061/86, 143371/86, and 230760/87, and are described to exhibit leukotriene antagonism, phospholipase inhibitory activity, 5α reductase inhibitory activity, aldose-reductase inhibitory activity, and the like.

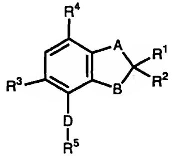
WO92-01681 and WO92-12144 disclose benzofuran and benzopyran derivatives which exhibit acyl-CoA acetyltransferase (ACAT) inhibitory activity.

WO93-01169 discloses benzofuran derivatives which exhibit tachykinin antagonism.

EP0307172 and US4910193 disclose benzofuran derivatives which exhibit antagonistic activity against serotonin $(5HT)_3$ receptors.

Disclosure of the Invention

The present invention relates to oxygen-containing heterocyclic compounds represented by following Formula (I):



(I)

wherein R^1 and R^2 independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or innsubstituted aromatic heterocyclic group, aralkyl, cyano, or $-(CH_2)_n-E^1-CO-G^1$ [wherein E^1 represents a bond, O, or NH; and G^1 represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, aralkyl, OR^6 (wherein R^6 represents hydrogen, lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or aralkyl), or NR^7R^8 (wherein R^7 and R^8 independently represent hydrogen, lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, substituted or unsubstituted aralkyl, or heteroarylalkyl; or R^7 and R^8 are combined to represent a substituted or unsubstituted heterocyclic group containing a nitrogen atom); and n represents an integer of 0 to 4]; R^1 and R^2 are combined to represent a saturated carbon ring together with a carbon atom adjacent thereto; or R^2, and R^{11} or R^{13} described below are combined to form a single bond; R^3 represents hydrogen, phenyl, or halogen; R^4 represents hydroxy or substituted or unsubstituted lower alkoxy; A represents $-C(R^9)(R^{10})-$ (wherein R^9 and R^{10} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, or polycycloalkyl) or O; B represents O, NR^{11} [wherein R^{11} represents hydrogen, lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, aralkyl, or $-(CH_2)_m-E^2-CO-G^2$ (wherein E^2, G^2, and m have the same meanings as the above-described E^1, G^1, and n, respectively); or R^{11} and R^2 are combined to form a single bond], $-C(R^{12})(R^{13})-$ [wherein R^{12} and R^{13} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, aralkyl, cyano, or $-(CH_2)_p-E^3-CO-G^3$ (wherein E^3, G^3, and p have the same meanings as the above-described E^1, G^1, and n, respectively); R^{13} and R^2 are combined to form a single bond; or R^{13} and R^2 are combined to form a saturated carbon ring together with two carbon atoms adjacent thereto]; or $-C(R^{14})(R^{15})-C(R^{16})(R^{17})-$ [wherein R^{14} and R^{15} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, aralkyl, substituted or unsubstituted aryl, or a substituted or unsubstituted aromatic heterocyclic group; or R^{14} and R^{15} are combined to form O; and R^{16} and R^{17} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, aralkyl, substituted or unsubstituted aryl, or a substituted or unsubstituted aromatic heterocyclic group; or R^{17} and R^{15} are combined to form a single bond; or R^{17} and R^{15} are combined to form a saturated carbon ring together with two carbon atoms adjacent thereto]; D represents (i) $-C(R^{18})(R^{19})-X-$ [wherein R^{18} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, hydroxy, substituted or unsubstituted lower alkoxy, or lower alkanoyloxy; and R^{19} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, hydroxy, substituted or unsubstituted lower alkoxy, lower alkanoyloxy, lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, or cyano; or R^{18} and R^{19} are combined to form O, S, or NR^{20} (wherein R^{20} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, hydroxy, substituted or unsubstituted lower alkoxy, or lower alkanoyloxy); X represents $-C(R^{21})(R^{22})-$ (wherein R^{21} and R^{22} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubsti-

tuted aromatic heterocyclic group, lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, or cyano) or S; or X represents NR^{23} (wherein R^{23} represents hydrogen, lower alkyl, cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or aralkyl) unless R^1 and R^2 simultaneously represent substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, or cycloalkenyl included in the above definition], (ii) -$C(R^{19a})$=Y- [wherein R^{19a} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, hydroxy, substituted or unsubstituted lower alkoxy, lower alkanoyloxy, lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, or cyano; and Y represents -$C(R^{24})$-Z-(wherein R^{24} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, or cyano; or R^{24} and R^{19a} are combined to form a single bond; and Z represents CONH, $CONHCH_2$, or a bond) or N], or (iii) a bond; and R^5 represents substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, cycloalkyl, pyridine-N-oxide, cyano, or lower alkoxycarbonyl; or pharmaceutically acceptable salts thereof. Hereinafter, the compounds represented by Formula (I) are referred to as Compounds (I). The same applies to the compounds of other formula numbers.

In the definitions of the groups in Formula (I), the lower alkyl and the lower alkyl moiety of the lower alkoxy, the lower alkanoyloxy, the lower alkanoyl, the lower alkoxycarbonyl, and the heteroarylalkyl include straight-chain or branched alkyl groups having 1 to 8 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, and octyl; the cycloalkyl and the cycloalkyl moiety of the cycloalkanoyl include cycloalkyl groups having 3 to 10 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, and cyclodecyl; and the polycycloalkyl includes polycycloalkyl groups having 4 to 12 carbon atoms, such as bicyclo[3.2.1]octyl, bicyclo[4.3.2]undecyl, adamantyl, and noradamantyl. The lower alkenyl includes straight-chain or branched alkenyl groups having 2 to 8 carbon atoms, such as vinyl, 1-propenyl, allyl, methacryl, 1-butenyl, crotyl, pentenyl, isoprenyl, hexenyl, heptenyl, and octenyl; and the cycloalkenyl includes cycloalkenyl groups having 4 to 10 carbon atoms, such as cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, and cyclodecenyl. The aryl includes phenyl and naphthyl; and the aralkyl includes aralkyl groups having 7 to 15 carbon atoms, such as benzyl, phenethyl, benzhydryl, and naphthylmethyl. The aromatic heterocyclic group and the heteroaryl moiety of the heteroarylalkyl include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, thienyl, furyl, thiazolyl, oxazolyl, indolyl, indazolyl, benzimidazolyl, benzotriazolyl, and purinyl. The heterocyclic group containing a nitrogen atom includes pyrrolidinyl, piperidino, piperazinyl, morpholino, thiomorpholino, homopiperidino, homopiperazinyl, tetrahydropyridinyl, tetrahydroquinolinyl, and tetrahydroisoquinolinyl; and the saturated carbon ring together with two adjacent carbon atoms includes groups having 3 to 10 carbon atoms, such as cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, cyclononane, and cyclodecane. The halogen includes a fluorine, chlorine, bromine, and iodine atom.

The substituted lower alkyl has the same or different 1 to 2 substituents such as cycloalkyl, which has the same meaning as defined above.

The substituted aryl, substituted aromatic heterocyclic group, and substituted aralkyl each has the same or different 1 to 3 substituents such as lower alkyl, hydroxy, lower alkoxy, lower alkanoyl, lower alkoxycarbonyl, carboxyl, aminocarbonyl, trifluoromethyl, amino, cyano, nitro, and halogen. The lower alkyl, lower alkoxy, lower alkanoyl, lower alkoxycarbonyl, and halogen each has the same meaning as defined above.

The substituted heterocyclic group containing a nitrogen atom has the same or different 1 to 3 substituents such as lower alkyl, cycloalkyl, aryl, and aralkyl. The lower alkyl, cycloalkyl, aryl, and aralkyl each has the same meaning as defined above.

The substituted lower alkoxy has the same or different 1 to 3 substituents such as halogen, which has the same meaning as defined above.

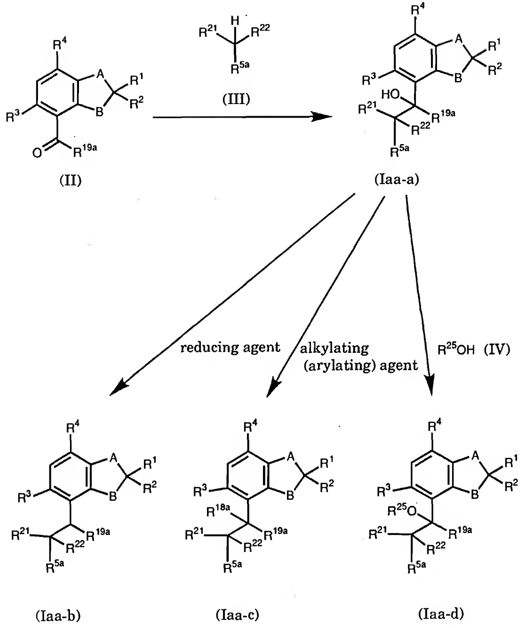
The pharmaceutically acceptable salts of Compounds (I) include pharmaceutically acceptable acid addition salts, metal salts, ammonium salts, and organic amine addition salts.

The pharmaceutically acceptable acid addition salts of Compounds (I) include inorganic acid addition salts such as hydrochloride, sulfate, nitrate, and phosphate, and organic acid addition salts such as acetate, maleate, fumarate, and citrate; the pharmaceutically acceptable metal salts include alkali metal salts such as sodium salt and potassium salt, alkaline earth metal salts such as magnesium salt and calcium salt, aluminium salt; and zinc salt; the pharmaceutically acceptable ammonium salts include ammonium and tetramethylammonium; and the pharmaceutically acceptable organic amine addition salts include addition salts with morpholine and piperidine.

Processes for preparing Compound (I) are described below.

Manufacturing method 1: Compound (Ia), which is Compound (I) in which D is (i) -$C(R^{18})(R^{19})$-X- and R^5 is substituted or unsubstituted aryl or a substituted or unsubstituted aromatic heterocyclic group, can be obtained according to the following Processes 1-1 to 1-13.

Process 1-1: Compound (Iaa), which is Compound (Ia) in which X is -$C(R^{21})(R^{22})$-, and R^{18} and R^{19} are not combined to form O, S, or NR^{20}, can be prepared according to the following reaction steps:



(In the formulae, R^{5a} is substituted or unsubstituted aryl or a substituted or unsubstituted aromatic heterocyclic group in the definition of R^5; R^{18a} is a group other than hydrogen, hydroxy, substituted or unsubstituted lower alkoxy, and lower alkanoyloxy in the definition of R^{18}, and R^{18a} and R^{19} are not combined to form O, S, or NR^{20}; R^{25} is substituted or unsubstituted lower alkyl or lower alkanoyl; and A, B, R^1, R^2, R^3, R^4, R^{19a}, R^{21}, and R^{22} each has the same meaning as defined above.)

The substituted or unsubstituted lower alkyl and lower alkanoyloxy in the definition of R^{25} each has the same meaning as defined above.

The starting Compound (II) can be obtained according to the known methods (J. Org. Chem., 1987, 52, 4072, Org. Prep. Proced. Int., 1989, 21, 763, Synthesis, 1978, 886, Arzneim.-Forsch., 1971, 21, 204, WO93/18024, WO94/12461) or the methods described in Reference Examples. In addition, the starting Compound (III) is commercially available, or,

if the starting Compound (III) is a picoline derivative, it can be obtained according to a known method (WO94/20455) or a similar method thereto.

Compound (Iaa-a), which is Compound (Iaa) in which R^{18} is hydroxy, can be obtained by treating Compound (III) with a base in an inert solvent at the temperature between -100°C and room temperature for 5 minutes to 10 hours, followed by reaction with a starting Compound (II) at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 30 hours.

Examples of the base are sodium hydroxide, potassium hydroxide, sodium methoxide, potassium ethoxide, sodium hydride, potassium hydride, butyl lithium, lithium diisopropylamide (LDA), potassium tert-butoxide, triethylamine, diisopropylethylamine, tributylamine, dicyclohexylmethylamine, N-methylmorphorine, N-methylpiperidine, diazabicycloundecene (DBU), and diazabicyclononene (DBN).

Examples of inert solvent are tetrahydrofuran (THF), dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, methanol, ethanol, butanol, isopropanol, dichloromethane, chloroform, benzene, toluene, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO).

Compound (Iaa-b), which is Compound (Iaa) in which R^{18} is hydrogen, can be obtained by treating Compound (Iaa-a) with a reducing agent in the presence or absence of a catalytic amount to a largely excess amount of an acid catalyst in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 48 hours.

Examples of the acid catalyst are p-toluenesulfonic acid, methanesulfonic acid, hydrochloric acid, trifluoroacetic acid, boron trifluoride, aluminium chloride, stannic chloride, titanium tetrachloride, zinc chloride, and ferric chloride.

Examples of the reducing agent are triethylsilane, tributylsilane, dimethylphenylsilane, and trichlorosilane.

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, dichloromethane, chloroform, benzene, and toluene.

Compound (Iaa-ba), which is Compound (Iaa-b) in which R^{22} is hydrogen, can also be obtained by treating Compound (Iba) prepared by the method described below (Process 2-2) with a reducing agent in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 30 hours, or by subjecting Compound (Iba) to hydrogenation in the presence of a catalyst in an inert solvent at the temperature between room temperature and the boiling point of the employed solvent for 5 minutes to 30 hours. An example of the reducing agent is sodium borohydride; examples of the catalyst for the hydrogenation are palladium/carbon, palladium, platinum dioxide, and Raney nickel; and examples of the inert solvent are THF, dioxane, methanol, ethanol, butanol, and isopropanol.

Compound (Iaa-c), which is Compound (Iaa) in which R^{18} is a group other than hydrogen, hydroxy, substituted or unsubstituted lower alkoxy, and lower alkanoyloxy in the definition of R^{18}, and R^{18} and R^{19} are not combined to form O, S, or NR^{20}, can be obtained by reacting Compound (Iaa-a) with an alkylating (arylating) agent in the presence of an acid catalyst in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 30 hours.

Examples of the alkylating (arylating) agent are various kinds of alkyl- or arylmagnesium bromides, alkyl-or arylmagnesium chlorides, alkyl- or arylmagnesium iodides, trialkylaluminium, tetraalkyltitanium, dialkyltitanium chloride, Tebbe reagent, and trialkylsilylnitrile.

Examples of the acid catalyst are boron trifluoride, aluminium chloride, stannic chloride, titanium tetrachloride, zinc chloride, and ferric chloride.

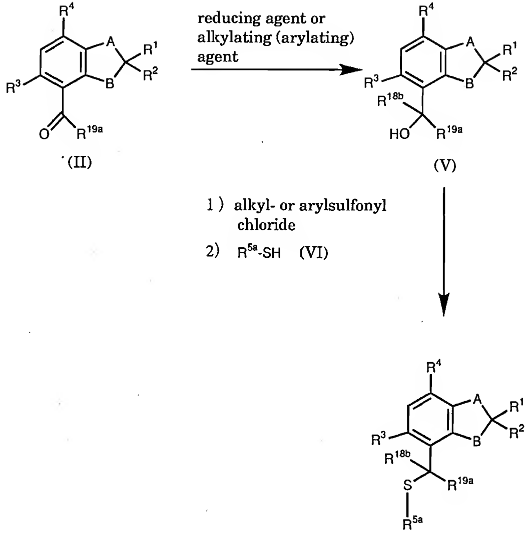
Examples of the inert solvent are THF, dioxane, diethyl ether, glyme, diglyme, dichloromethane, chloroform, benzene, and toluene.

Compound (Iaa-d), which is Compound (Iaa) in which R^{18} is substituted or unsubstituted lower alkoxy or lower alkanoyloxy, can be obtained by reacting Compound (Iaa-a) with Compound (IV) in the presence of an acid catalyst in an inert solvent or without a solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 48 hours.

Examples of the acid catalyst are p-toluenesulfonic acid, methanesulfonic acid, hydrochloric acid, sulfuric acid, and trifluoroacetic acid.

Examples of the inert solvent are THF, dioxane, diethyl ether, glyme, diglyme, dichloromethane, chloroform, benzene, toluene, DMF, and DMSO.

Process 1-2: Compound (Iab), which is Compound (Ia) in which X is S, and R^{18} and R^{19} are not combined to form O, S, or NR^{20}, can be prepared by the following reaction steps:



(II) (V) (Iab)

(In the formulae, R^{18b} is a group other than hydroxy, substituted or unsubstituted lower alkoxy, and lower alkanoyloxy in the definition of R^{18}, and R^{18b} and R^{19} are not combined to form O, S, or NR^{20}; and A, B, R^1, R^2, R^3, R^4, R^{5a}, and R^{19a} each has the same meaning as defined above.)

Compound (Va), which is Compound (V) in which R^{18b} is hydrogen, can be obtained by treating Compound (II) with a reducing agent in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 30 hours.

Examples of the reducing agent are lithium aluminium hydride and sodium borohydride.

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, methanol, ethanol, butanol, isopropanol, dichloromethane, chloroform, benzene, and toluene.

Compound (Vb), which is Compound (V) in which R^{18b} is a group other than hydrogen in the definition of R^{18b}, can be obtained by reacting Compound (II) with an alkylating (arylating) agent in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 30 hours.

Examples of the alkylating (arylating) agent are various kinds of alkyl- or arylmagnesium bromides, alkyl-or arylmagnesium chlorides, alkyl- or arylmagnesium iodides, and various kinds of alkyl or aryl lithiums.

Examples of the inert solvent are THF, dioxane, diethyl ether, glyme, diglyme, methanol, ethanol, butanol, isopro-

panol, dichloromethane, chloroform, benzene, and toluene.

Compound (Iab) can be obtained by reacting Compound (V) with, for example, alkyl- or arylsulfonyl chloride, in the presence of a base in an inert solvent at the temperature between -20°C and 0°C for 5 minutes to 5 hours, followed by reaction with Compound (VI) at the temperature between 0°C and the boiling point of the employed solvent for 5 minutes to 48 hours.

Examples of the base are sodium hydride, potassium hydride, butyl lithium, LDA, potassium tert-butoxide, triethylamine, diisopropylethylamine, tributylamine, dicyclohexylmethylamine, N-methylmorphorine, N-methylpiperidine, DBU, and DBN.

Examples of the alkyl- or arylsulfonyl chloride are methanesulfonyl chloride, benzenesulfonyl chloride, and p-toluenesulfonyl chloride.

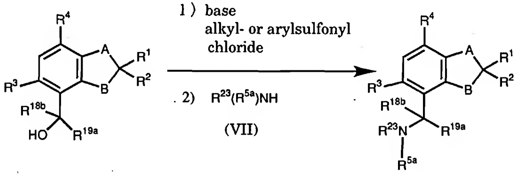
Examples of the inert solvent are THF, dioxane, diethyl ether, glyme, diglyme, dichloromethane, chloroform, benzene, toluene, DMF, and DMSO.

Alternatively, Compound (Iab) can also be obtained by reacting Compound (V) with Compound (VI) in the presence of an acid catalyst in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 48 hours.

Examples of the acid catalyst are p-toluenesulfonic acid, methanesulfonic acid, hydrochloric acid, trifluoroacetic acid, boron trifluoride, aluminium chloride, stannic chloride, titanium tetrachloride, zinc chloride, and ferric chloride.

Examples of the inert solvent are THF, dioxane, diethyl ether, glyme, diglyme, dichloromethane, chloroform, benzene, and toluene.

Process 1-3: Compound (Iac), which is Compound (Ia) in which X is NR^{23}, and R^{18} and R^{19} are not combined to form O, S, or NR^{20}, can be prepared by the following reaction step:

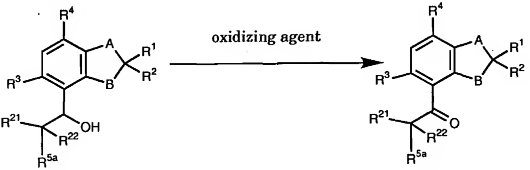


(V) (Iac)

(In the formulae, A, B, R^1, R^2, R^3, R^4, R^{5a}, R^{18b}, R^{19a}, and R^{23} each has the same meaning as defined above.)

Compound (Iac) can be obtained according to the method described in Process 1-2 in which Compound (Iab) is obtained from Compound (V) and Compound (VI), using Compound (VII) instead of Compound (VI).

Process 1-4: Compound (Iad), which is Compound (Ia) in which D is $-C(=O)-C(R^{21})(R^{22})-$, can be prepared by the following reaction step:



(Iaa-aa) (Iad)

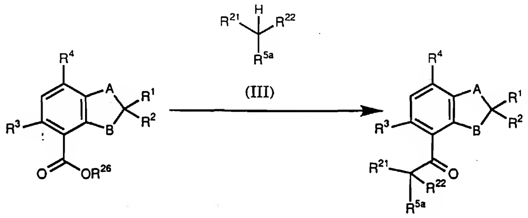
(In the formulae, R^1, R^2, R^3, R^4, R^{5a}, R^{21}, and R^{22} each has the same meaning as defined above.)

Compound (Iad) can be obtained by treating Compound (Iaa-aa), which is Compound (Iaa-a) in which R^{19a} is hydrogen, with an oxidizing agent in an inert solvent containing water at the temperature between 0°C and the boiling point of the employed solvent for 5 minutes to 72 hours.

Examples of the oxidizing agent are manganese dioxide, potassium permanganate, pyridinium chlorochromate (PCC), and pyridinium dichromate (PDC).

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, acetone, methyl vinyl ketone, dichloromethane, chloroform, benzene, toluene, DMF, and DMSO.

Process 1-5: Compound (Iad) can also be prepared according to the following reaction step:

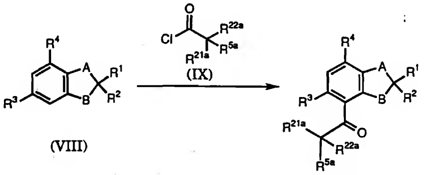


(IIa) (Iad)

(In the formulae, R^{26} is substituted or unsubstituted lower alkyl; and A, B, R^1, R^2, R^3, R^4, R^{5a}, R^{21}, and R^{22} each has the same meaning as defined above.)

Compound (Iad) can be obtained according to the method described in Process 1-1 in which Compound (Iaa-a) is obtained from Compound (II) and Compound (III), using Compound (IIa), which is a starting Compound (II) in which R^{19a} is substituted or unsubstituted lower alkoxy.

Process 1-6: Compound (Iad-a), which is Compound (Iad) in which R^{21} and R^{22} are groups other than lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, and cyano in the definition of R^{21} and R^{22}, can also be prepared by the following reaction step:



(VIII) (Iad-a)

(In the formulae, R^{21a} and R^{22a} are groups other than lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, and cyano in the definition of R^{21} and R^{22}; and A, B, R^1, R^2, R^3, R^4, and R^{5a} each has the same meaning as defined above.)

The starting Compound (VIII) can be obtained according to the methods described in Reference Examples or similar methods thereto.

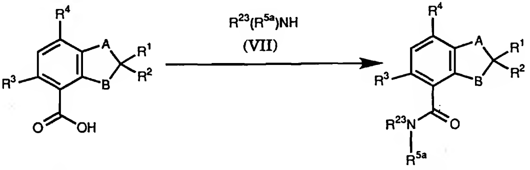
Compound (Iad-a) can be obtained by reacting Compound (VIII) with Compound (IX) in the presence of an acid cat-

alyst in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 30 hours.

Examples of the acid catalyst are boron trifluoride, aluminium chloride, stannic chloride, titanium tetrachloride, zinc chloride, and ferric chloride.

Examples of the inert solvent are THF, dioxane, diethyl ether, glyme, diglyme, dichloromethane, 1,2,-dichloroethane, chloroform, benzene, nitrobenzene, and toluene.

Process 1-7: Compound (Iae), which is Compound (Ia) in which D is $-C(=O)-NR^{23}-$, can be prepared by the following reaction step:



(IIb) (Iae)

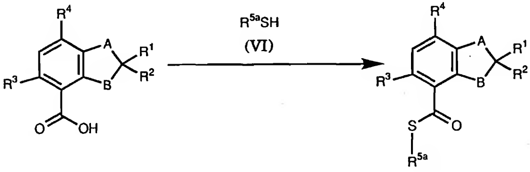
(In the formulae, A, B, R^1, R^2, R^3, R^4, R^{5a}, and R^{23} each has the same meaning as defined above.)

The desired Compound (Iae) can be obtained by dehydrative condensation of Compound (IIb), which is a starting Compound (II) in which R^{19a} is hydroxy, and Compound (VII). For the above condensation, numerous methods are known and applicable, as described in Jikken Kagaku Koza, 22, 137-172, the 4th edition (Nippon Kagaku-Kai, 1992). For example, Compound (IIb) is treated with one equivalent to a largely excess amount of thionyl chloride, phosphorus pentachloride, oxalyl chloride, or the like, if necessary in the presence of a catalytic amount to 20 equivalents of a base, in an inert solvent at the temperature between 0°C and the boiling point of the employed solvent for 0.1 to 48 hours to give a corresponding acid chloride. Then, the desired Compound (Iae) can be obtained by reacting the obtained acid chloride with 0.5 to 50 equivalents of Compound (VII), if necessary in the presence of 0.5 equivalent to a largely excess amount of a base, in an inert solvent at the temperature between 0°C and the boiling point of the employed solvent for 0.1 to 48 hours.

Examples of the base are those which are used in the manufacturing method for Compound (Iaa-a) described in Process 1-1.

Examples of the inert solvents are dichloromethane, chloroform, benzene, toluene, THF, dioxane, DMF, and DMSO.

Process 1-8: Compound (Iaf), which is Compound (Ia) in which D is $-C(=O)-S-$, can be prepared by the following reaction step:

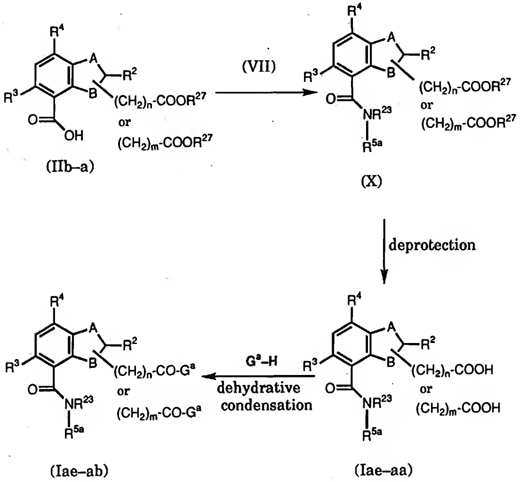


(IIb) (Iaf)

(In the formulae, A, B, R^1, R^2, R^3, R^4, and R^{5a} each has the same meaning as defined above.)

Compound (Iaf) can be obtained according to the method described in Process 1-7 in which Compound (Iae) is obtained from Compound (IIc) and Compound (VII), using Compound (VI) instead of Compound (VII).

Process 1-9: Compound (Iae-a), which is Compound (Iae) in which one of R^1 and R^{11} (or R^{13}) is $-(CH_2)_n$-CO-G^1 or $-(CH_2)_m$-CO-G^2, can be prepared by the following reaction steps:



[In the formulae, G^a is OR^6 (with the proviso that R^6 is not hydrogen) or NR^7R^8 in the definition of G^1 (or G^2); R^{27} is a protective group of a carboxyl group; and A, B, R^2, R^3, R^4, R^{5a}, R^{23}, n, and m each has the same meaning as defined above.]

A protective group for a carboxyl group is generally required to be deprotected selectively compared with an amide bond for converting a protected carboxyl group to a carboxyl group, and those which are described in the fifth chapter of Protective Group in Organic Synthesis (the second edition, Green and Watt, Jon Weary and Suns Incorporated, 1991) can be applied. Examples of these are esters of substituted or unsubstituted lower alkyl including methyl, ethyl, and tert-butyl, benzyl, allyl, and 2-(trimethylsilyl)ethyl.

The starting Compound (IIb-a) can be obtained according to the methods described in Reference Examples or similar methods thereto.

Compound (X) can be obtained according to the method described in Process 1-7, using Compound (IIb-a) and Compound (VII).

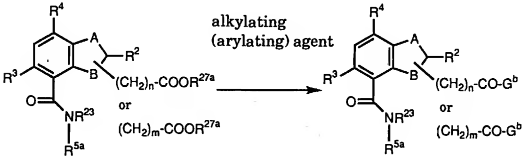
Compound (Iae-aa), which is Compound (Iae-a) in which G^1 (or G^2) is hydroxy, can be obtained by treating Compound (X) in the presence of a catalytic to largely excess amount of a base in an inert solvent containing water at the temperature between room temperature and the boiling point of the employed solvent for 0.1 to 48 hours.

Examples of the base are those which are mentioned in Process 1-7; and examples of the inert solvent are THF, dioxane, ethylene glycol, triethylene glycol, glyme, diglyme, methanol, ethanol, butanol, and isopropanol.

Compound (Iae-ab), which is Compound (Iae-a) in which G^1 (or G^2) is OR^6 (with the proviso that R^6 is not hydro-

gen) or NR^7R^8 in the definition of G^1 (or G^2), can be obtained according to the method described in Process 1-7, using Compound (Iae-aa) and Compound G^a-H.

Process 1-10: Compound (Iae-ac), which is Compound (Iae-a) in which G^1 (or G^2) is substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or aralkyl in the definition of G^1 (or G^2), can be prepared by the following reaction step:



(Xa) (Iae–ac)

[In the formulae, R^{27a} is substituted or unsubstituted lower alkyl; G^b is substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or aralkyl in the definition of G^1 (or G^2); and A, B, R^2, R^3, R^4, R^{5a}, R^{23}, n, and m each has the same meaning as defined above.]

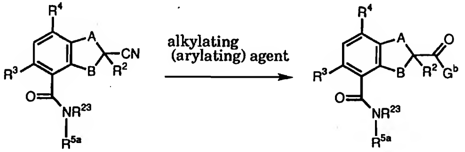
The substituted or unsubstituted lower alkyl in the definition of R^{27a} has the same meaning as defined above.

Compound (Iae-ac) can be obtained by reacting Compound (Xa), which is Compound (X) in which R^{27} is substituted or unsubstituted lower alkyl, with an alkylating (arylating) agent in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 30 hours.

Examples of the alkylating (arylating) agent are various kinds of alkyl- or arylmagnesium bromides, alkyl-or arylmagnesium chlorides, alkyl- or arylmagnesium iodides, and various kinds of alkyl or aryl lithium.

Examples of the inert solvent are THF, dioxane, diethyl ether, glyme, diglyme, methanol, ethanol, butanol, isopropanol, dichloromethane, chloroform, benzene, and toluene.

Process 1-11: Compound (Iae-aca), which is Compound (Iae-ac) in which one of R^1 and R^{11} (or R^{13}) is -CO-G^b, can also be prepared by the following reaction step:

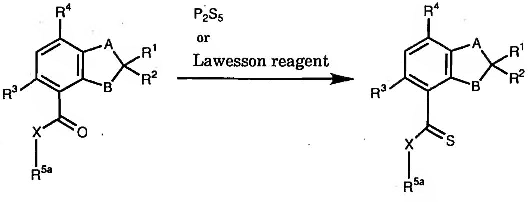


(Iae-b) (Iae–aca)

(In the formulae, A, B, R^2, R^3, R^4, R^{5a}, R^{23}, and G^b each has the same meaning as defined above.)

Compound (Iae-aca) can be obtained according to the method described in Process 1-10 from Compound (Iae-b), which is Compound (Iae) in which R^1 is cyano.

Process 1-12: Compound (Iag), which is Compound (Ia) in which D is -C(=S)-X-, can be prepared by the following reaction step:



(Iad), (Iae) or (Iaf)

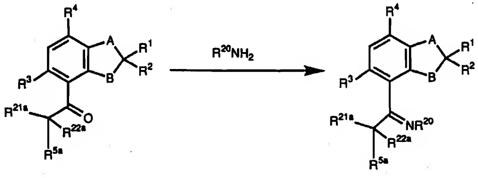
(Iag)

(In the formulae, A, B, R^1, R^2, R^3, R^4, R^{5a}, and X each has the same meaning as defined above.)

Compound (Iag) can be obtained by treating Compound (Iad), Compound (Iae), or Compound (Iaf) with phosphorus pentasulfide or Lawesson's reagent in an inert solvent at the temperature between room temperature and the boiling point of the employed solvent for 5 minutes to 72 hours.

Examples of inert solvent are pyridine, THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, dichloromethane, chloroform, benzene, toluene, xylene, DMF, and DMSO.

Process 1-13: Compound (Iah), which is Compound (Ia) in which D is -C(=NR^{20})-$CR^{21}R^{22}$-, can be prepared by the following reaction step:



(Iad-a)

(Iah-a)

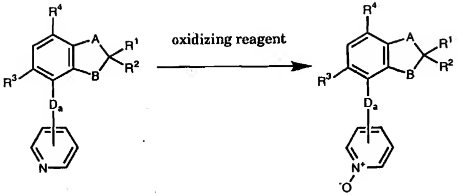
(In the formulae, A, B, R^1, R^2, R^3, R^4, R^{5a}, R^{20}, R^{21a}, and R^{22a} each has the same meaning as defined above.)

Compound (Iah-a), which is Compound (Iah) in which R^{21} and R^{22} are groups other than lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, and cyano in the definition of R^{21} and R^{22}, can be obtained by reacting Compound (Iad-a) with $R^{20}NH_2$ in the presence or absence of an acid catalyst in an inert solvent or without solvent at the temperature between room temperature and the boiling point of the employed solvent for 5 minutes to 48 hours.

Examples of the acid catalyst are p-toluenesulfonic acid, methanesulfonic acid, hydrochloric acid, sulfuric acid, acetic acid, and trifluoroacetic acid.

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, methanol, ethanol, isopropanol, tert-butanol, dichloromethane, chloroform, benzene, toluene, DMF, DMSO, and pyridine.

Process 1-14: Compound (Ia'), which is Compound (I) in which D is (i) -C(R^{18})(R^{19})-X- and R^5 is pyridine-N-oxide, can be prepared by the following reaction step:



(Iaa), (Iad) or (Iae)

(Ia'a)

[In the formulae, D^a is D in Compound (Iaa), (Iad), and (Iae); and A, B, R^1, R^2, R^3, and R^4 each has the same meaning as defined above.]

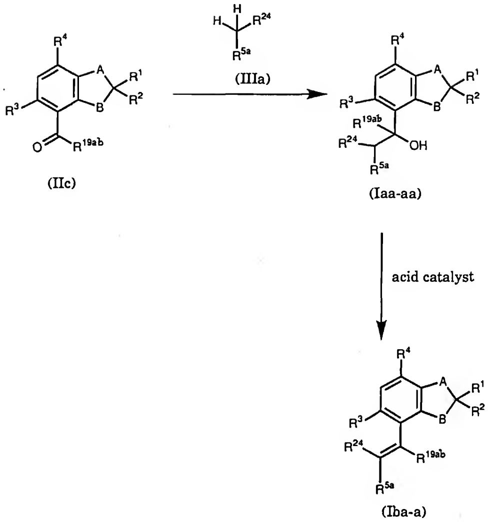
Compound (Ia'a), which is Compound (Ia') in which D is D in Compound (Iaa), (Iad), and (Iae) in the definition of D, can be obtained by treating Compound (Iaa), (Iad), or (Iae) with an oxidizing agent in an inert solvent at the temperature between room temperature and the boiling point of the employed solvent for 5 minutes to 72 hours.

Examples of inert solvent are dichloromethane, chloroform, benzene, toluene, xylene, DMF, DMSO, and acetic acid.

Examples of the oxidizing agent are peracetic acid, trifluoroperacetic acid, metachloroperbenzoic acid, hydrogen peroxide, benzoyl peroxide, tert-butyl hydroperoxide, and tert-amyl hydroperoxide.

Manufacturing method 2: Compound (Ib), which is Compound (I) in which D is (ii) $-C(R^{19a})=Y-$, can be obtained by the following Processes 2-1 to 2-5.

Process 2-1: Compound (Iba-a), which is Compound (Ib) in which Y is $-CR^{24}$, R^5 is substituted or unsubstituted aryl, or a substituted or unsubstituted aromatic heterocyclic group, and R^{24} and R^{19a} are not combined to form a single bond, can be prepared by the following reaction steps:



(In the formulae, R^{19ab} is a group other than hydroxy, and substituted or unsubstituted lower alkoxy in the definition as R^{19a}; and A, B, R^1, R^2, R^3, R^4, R^{5a}, R^{19a}, and R^{24} each has the same meaning as defined above.)

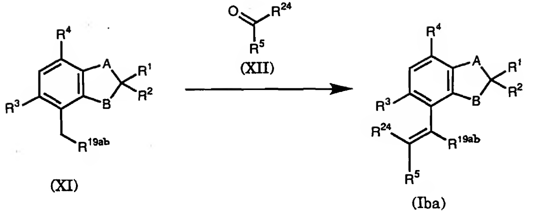
Compound (Iaa-aa), which is Compound (Iaa-a) in which R^{22} is hydrogen, can be obtained according to the method similar to the manufacturing method for Compound (Iaa-a) described in Process 1-1, using Compound (IIc) and Compound (IIIa), which is Compound (III) in which R^{22} is hydrogen. Compound (Iaa-aa) is directly converted to Compound (Iba-a) without isolation when R^{24} is lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, or cyano.

Compound (Iba-a) can be obtained by treating Compound (Iaa-aa) in the presence an acid catalyst in an inert solvent at the temperature between room temperature and the boiling point of the employed solvent for 5 minutes to 48 hours.

Examples of the acid catalyst are p-toluenesulfonic acid, methanesulfonic acid, hydrochloric acid, sulfuric acid, acetic acid, and trifluoroacetic acid.

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, dichloromethane, chloroform, benzene, toluene, DMF, and DMSO.

Process 2-2: Compound (Iba), which is Compound (Ib) in which Y is $-CR^{24}$, and R^{24} and R^{19a} are not combined to form a single bond, can also be prepared by the following reaction step:



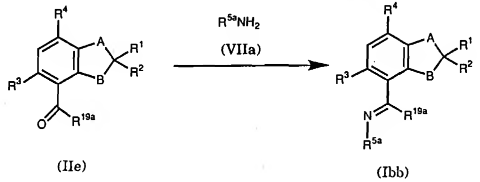
(In the formulae, A, B, R^1, R^2, R^3, R^4, R^5, R^{19ab}, and R^{24} each has the same meaning as defined above.)

The starting compound (XI) can be obtained according to the methods described in Reference Examples or similar methods thereto.

Compound (Iba) can be obtained by treating starting Compound (XI) with a base in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 10 hours, followed by reaction with Compound (XII) at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 30 hours.

Examples of the base and the inert solvent are those used in the manufacturing method for Compound (Iaa-a) described in Process 1-1.

Process 2-3: Compound (Ibb), which is Compound (Ib) in which Y is N, and R^5 is substituted or unsubstituted aryl or a substituted or unsubstituted aromatic heterocyclic group, can be prepared by the following reaction step:



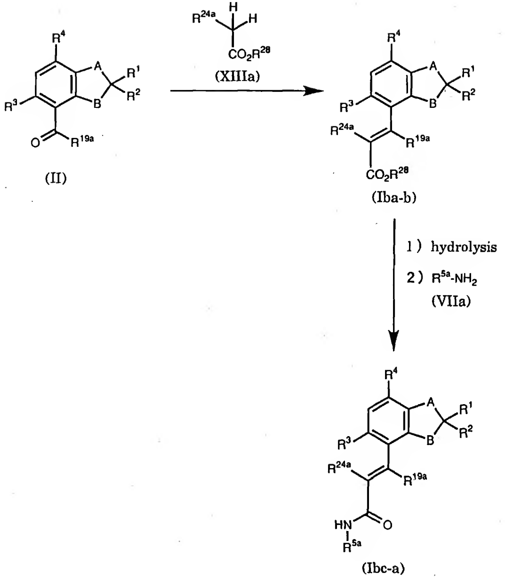
(In the formulae, A, B, R^1, R^2, R^3, R^4, R^{5a}, and R^{19a} each has the same meaning as defined above.)

Compound (Ibb) can be obtained by reacting Compound (IIe) with Compound (VIIa), which is Compound (VII) in which R^{23} is hydrogen, in the presence of an acid catalyst in an inert solvent or without solvent at the temperature between room temperature and the boiling point of the employed solvent for 5 minutes to 48 hours.

Examples of the acid catalyst are p-toluenesulfonic acid, methanesulfonic acid, hydrochloric acid, sulfuric acid, acetic acid, and trifluoroacetic acid.

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, methanol, ethanol, isopropanol, tert-butanol, dichloromethane, chloroform, benzene, toluene, DMF, and DMSO.

Process 2-4: Compound (Ibc), which is Compound (Ib) in which Y is $-CR^{24}-CONH-$, and R^5 is substituted or unsubstituted lower aryl or a substituted or unsubstituted aromatic heterocyclic group, can be prepared by the following reaction steps:



(In the formulae, R^{28} is lower alkyl; R^{24a} is a group other than lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, and cyano in the definition as R^{24}; and A, B, R^1, R^2, R^3, R^4, R^{5a}, and R^{19a} each has the same meaning as defined above.)

The lower alkyl in the definition of R^{28} has the same meaning as defined above.

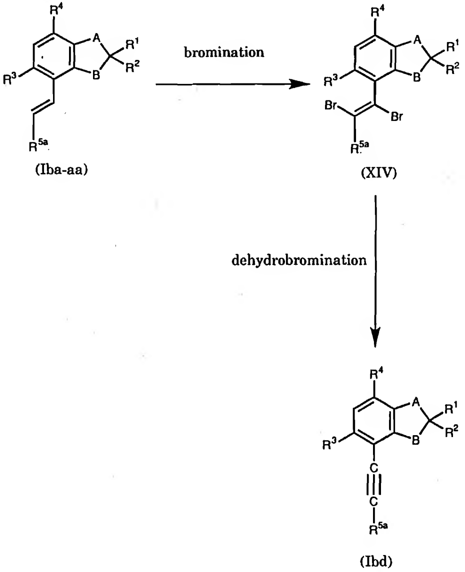
Compound (Iba-b), which is Compound (Iba) in which R^5 is lower alkoxycarbonyl and R^{24} is a group other than lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, and cyano, can be obtained according to the method similar to the manufacturing method for Compound (Iba-a) described in Process 2-1, using Compound (II) and Compound (XIII). Further, Compound (Iba-b) can be obtained by reacting Compound (II) with a corresponding diester of phosphorous acid treated with a base in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 48 hours.

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, methanol, ethanol, butanol, isopropanol, dichloromethane, chloroform, benzene, toluene, DMF, and DMSO.

Examples of the base are sodium hydroxide, potassium hydroxide, sodium methoxide, potassium ethoxide, sodium hydride, potassium hydride, butyl lithium, LDA, potassium tert-butoxide, triethylamine, diisopropylethylamine, tributylamine, dicyclohexylmethylamine, N-methylmorphorine, N-methylpiperidine, DBU, and DBN.

Compound (Ibc-a), which is Compound (Ibc) in which R^{24} is a group other than lower alkanoyl, cycloalkanoyl, lower

alkoxycarbonyl, and cyano, can be obtained according to the method described in Process 1-9 in which Compound (Iae-ab) is obtained from Compound (X), using Compound (Iba-b) and Compound (VIIa).
Process 2-5: Compound (Ibd), which is Compound (Ib) in which Y is -CR^{24}, R^{24} and R^{19a} are combined to form a single bond, and R^5 is substituted or unsubstituted aryl, or a substituted or unsubstituted aromatic heterocyclic group, can be prepared by the following reaction steps:



(In the formulae, A, B, R^1, R^2, R^3, R^4, and R^{5a} each has the same meaning as defined above.)

Compound (XIV) can be obtained by treating Compound (Iba-aa), which is Compound (Iba-a) in which R^{19a} and R^{24} are both hydrogen, with a brominating agent in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 10 hours.

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, methanol, ethanol, isopropanol, tert-butanol, dichloromethane, chloroform, benzene, toluene, DMF, and DMSO.

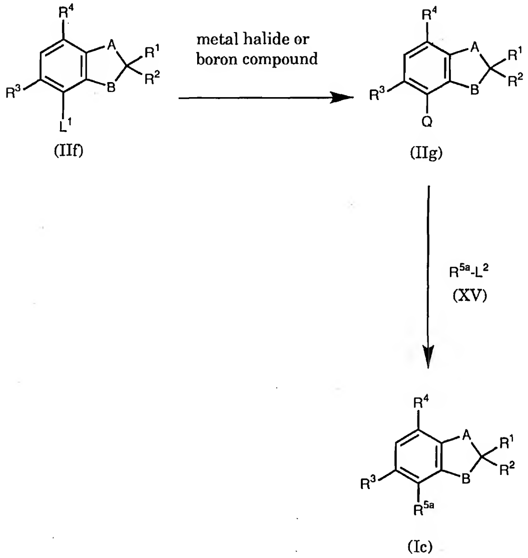
Examples of the brominating agent are bromine, tetrabutylammonium tribromide, tetramethylammonium tribromide, pyridinium tribromide, NBS, and copper bromide.

Compound (Ibd) can be obtained by treating Compound (XIV) with a base in an inert solvent at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 10 hours.

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, methanol, ethanol, isopropanol, tert-butanol, dichloromethane, chloroform, benzene, toluene, DMF, and DMSO.

Examples of the base are potassium hydroxide, sodium ethoxide, sodium methoxide, potassium tert-butoxide, and sodium amide.

Manufacturing method 3: Compound (Ic), which is Compound (I) in which D is (iii) a bond, and R^5 is substituted or unsubstituted aryl, or a substituted or unsubstituted aromatic heterocyclic group, can be obtained by the following process:



(In the formulae, L^1 and L^2 independently represent iodine, bromine, or chlorine; and A, B, R^1, R^2, R^3, R^4, and R^{5a} each has the same meaning as defined above.)

Examples of the metal halide are alkyltin halides such as tributyltin chloride and trimethyltin chloride, and zinc halides such as zinc chloride, zinc bromide, and zinc iodide; and examples of the boron compound are trimethoxy boron, phenylboric acid, and boric acid.

Compound (IIg) can be obtained by treating Compound (IIf) with a base in an inert solvent at the temperature between -100°C and room temperature for 5 minutes to 10 hours, followed by reaction with a metal halide or a boron compound at the temperature between -100°C and the boiling point of the employed solvent for 5 minutes to 30 hours.

Examples of the base are sodium hydroxide, potassium hydroxide, sodium methoxide, potassium ethoxide, sodium hydride, potassium hydride, butyl lithium, LDA, potassium tert-butoxide, triethylamine, diisopropylethylamine, trib-

utylamine, dicyclohexylmethylamine, N-methylmorphorine, N-methylpiperidine, DBU, and DBN.

Examples of the inert solvent are THF, dioxane, diethyl ether, ethylene glycol, triethylene glycol, glyme, diglyme, methanol, ethanol, butanol, isopropanol, dichloromethane, chloroform, benzene, toluene, DMF, and DMSO.

Compound (Ic) can be obtained by reacting Compound (IIg) with Compound (XV) in the presence of a catalytic to largely excess amount of a palladium complex in an inert solvent at the temperature between room temperature and the boiling point of the employed solvent for 5 minutes to 30 hours. Moreover, a salt such as lithium chloride, or an oxidizing agent such as silver oxide may be added, if necessary.

Examples of the inert solvent are THF, dioxane, diethyl ether, dichloromethane, chloroform, benzene, toluene, dimethylacetamide (DMA), DMF, and DMSO.

The intermediates and the desired compounds in the processes described above can be isolated and purified by purification methods conventionally used in organic synthetic chemistry, for example, filtration, extraction, washing, drying, concentration, recrystallization, and various kinds of chromatography. The intermediates may also be subjected to the subsequent reaction without isolation.

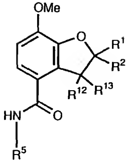
Compounds (I) can exist in the form of stereoisomers such as geometrical isomers and optical isomers, and the present invention covers all isomers including these isomers and mixtures thereof.

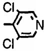
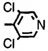
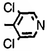
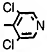
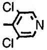
In the case where a salt of Compound (I) is desired and it is produced in the form of the desired salt, it can be subjected to purification as such. In the case where Compound (I) is produced in the free form and its salt is desired, Compound (I) is dissolved or suspended in a suitable solvent, followed by addition of an acid or a base to form a salt, which may be isolated and purified.

Compounds (I) and pharmaceutically acceptable salts thereof may be in the form of adducts with water or various solvents, which are also within the scope of the present invention.

Examples of Compound (I) obtained in the present invention are shown in Tables 1 to 8.

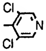
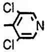
Table 1



Compd. No.	R^1	R^2	R^{13}	R^{12}	R^5
1	H	H	H	H	
2	H	H	H	Me	
3	H	H	H	Et	
4	H	H	H	i-Pr	
5	H	H	H	CH_2CO_2Et	
6	H	H	H	CH_2CO_2Et	

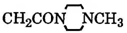
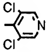
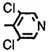
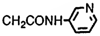
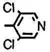
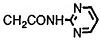
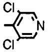
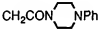
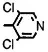
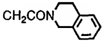
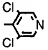
* In the Table, Me represents CH_3, Et represents C_2H_5, and i-Pr represents $(CH_3)_2CH$, respectively.

Table 1 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	R^5
7	H	H	H	CH_2CO_2Et	
8	H	H	H	CH_2CO_2Et	
9	H	H	H	CH_2CO_2H	
10	H	H	H	CH_2CO_2H	
11	H	H	H	CH_2CO_2H	
12	H	H	H	CH_2CO_2H	
13	H	H	H	$CH_2CO_2CH_2C_6H_5$	
14	H	H	H	$CH_2CO_2CH_2C_6H_5$	

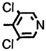
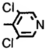
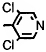
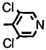
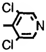
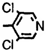
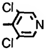
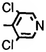
* In the Table, Et represents C_2H_5.

Table 1 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	R^5
15	H	H	H	$CH_2CO_2CH_2C_6H_5$	
16	H	H	H	$CH_2CO_2CH_2C_6H_5$	
17	H	H	H		
18	H	H	H		
19	H	H	H		
20	H	H	H		
21	H	H	H		
22	H	H	H		

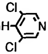
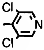
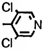
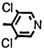
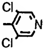
* In the Table, Ph represents C_6H_5.

Table 1 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	R^5
23	H	H	H	$CH_2CO_2CH_2CH_2C_6H_5$	
24	H	H	H	$CH_2CONHCH_2$- 	
25	H	H	H	$CH_2CONHCH_2C_6H_5$	
26	H	H	H	$CH_2CONHCH_2$- 	
27	H	H	H	$CH_2CONHC_6H_5$	
28	H	H	H	$CH_2CONHCH_2$-  OMe	
29	H	H	H	$CH_2CONHCH_2$-  F	
30	H	H	H	$CH_2CONHCH_2$-  Cl	

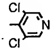
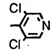
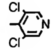
* In the Table, Me represents CH_3.

Table 1 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	R^5
31	H	H	H	$CH_2CONHCH_2$- 	
32	H	H	H	CH_2CONH- 	
33	H	single bond		H	
34	CN	single bond		H	
35	COC_6H_5	single bond		H	
36	n-Bu	single bond		H	
37	$CH_2C_6H_5$	single bond		H	
38		single bond		H	
39		single bond		H	
40		single bond		H	
41		single bond		H	

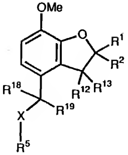
* In the Table, n-Bu represents $(CH_2)_3CH_3$.

Table 1 (continued)

Compd. No.	R^1	R^2 R^{13}	R^{12}	R^5
42	H	single bond	C_6H_5	
43	H	single bond	CH_2CO_2Et	
44	H	single bond	CH_2CO_2H	

* In the Table, Et represents C_2H_5.

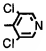
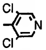
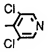
Table 2



Compd. No.	R^1	R^2	R^{13}	R^{12}	X	R^{18}	R^{19}	R^5
45	Me	Me	H	H	CH_2	H	H	
46	Me	Me	H	H	CH_2	H	H	
47	Me	Me	H	H	CH_2	H	Ph	
48	Me	Me	H	H	S	H	H	
49	Me	Me	H	H	S	H	Ph	
50	Et	Et	H	H	CH_2	H	H	
51	Et	Et	H	H	CH_2	H	H	
52	-$(CH_2)_4$-		H	H	CH_2	H	H	

* In the Table, Me represents CH_3, Et represents C_2H_5, and Ph represents C_6H_5, respectively.

Table 2 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	X	R^{18}	R^{19}	R^5
53	$-(CH_2)_4-$		H	H	CH_2	H	H	
54	$-(CH_2)_5-$		H	H	CH_2	H	H	
55	$-(CH_2)_5-$		H	H	CH_2	H	Ph	
56	H	H	H	Me	CH_2	H	H	
57	H	H	H	Me	CH_2	H	H	
58	H	H	H	Me	CH_2	H	Ph	
59	H	H	H	Me	S	H	H	
60A	H	H	H	Me	S	H	Ph	
60B	H	H	H	Me	S	H	Ph	
61	H	H	H	Me	NH	H	H	
62	Me	Me	H	H	CH_2	H	OMe	

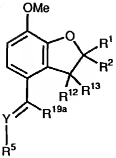
* In the Table, Me represents CH_3 and Ph represents C_6H_5, respectively.

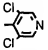
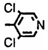
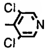
Table 2 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	X	R^{18}	R^{19}	R^5
63	Me	Me	H	H	CH_2	H	CN	
64	$-(CH_2)_4-$		H	H	CH_2	H	CN	
65	$-(CH_2)_4-$		H	H	CH_2	Me	CN	
66		single bond		H	CH_2	H	Ph	

* In the Table, Me represents CH_3 and Ph represents C_6H_5, respectively.

Table 3



Compd. No.	R^1	R^2	R^{13}	R^{12}	Y	R^{19a}	R^5
67	Me	Me	H	H	CH	H	
68	Me	Me	H	H	CH	H	
69	Me	Me	H	H	CH	Me	
70	Me	Me	H	H	CH	Ph	
71	Et	Et	H	H	CH	H	
72	Et	Et	H	H	CH	H	
73	-$(CH_2)_4$-		H	H	CH	H	
74	-$(CH_2)_4$-		H	H	CH	H	

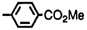
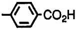
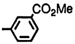
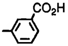
* In the Table, Me represents CH_3, Et represents C_2H_5, and Ph represents C_6H_5, respectively.

Table 3 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	Y	R^{19a}	R^5
75	$-(CH_2)_4-$		H	H	CH	Me	
76	$-(CH_2)_5-$		H	H	CH	H	
77	$-(CH_2)_5-$		H	H	CH	H	
78	H	H	H	Me	CH	H	
79	H	H	H	Me	CH	H	
80	H	H	H	Me	CH	Ph	
81	Ph	single bond		H	CH	H	
82		single bond		H	CH	H	
83		single bond		H	CH	H	
84		single bond		H	CH	H	
85		single bond		H	CH	H	

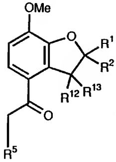
* In the Table, Me represents CH_3 and Ph represents C_6H_5, respectively.

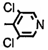
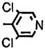
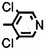
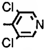
Table 3 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	Y	R^{19a}	R^5
86	Me	Me	H	H	CCN	H	
87	Me	Me	H	H	CCO_2Et	H	
88	Me	Me	H	H	CCN	H	CN
89	Me	Me	H	H	CCN	H	CO_2Et
90	$-(CH_2)_4-$		H	H	CHCONH	H	
91	$-(CH_2)_4-$		H	H	CHCONH	H	
92	$-(CH_2)_4-$		H	H	CHCONH	H	
93	$-(CH_2)_4-$		H	H	CHCONH	H	
94	$-(CH_2)_4-$		H	H	CHCONH	H	

* In the Table, Me represents CH_3 and Et represents C_2H_5, respectively.

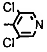
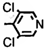
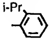
Table 4



Compd. No.	R^1	R^2	R^{13}	R^{12}	R^5
95	Me	Me	H	H	
96	Me	Me	H	H	
97	Et	Et	H	H	
98	Et	Et	H	H	
99	-$(CH_2)_4$-		H	H	
100	-$(CH_2)_4$-		H	H	
101	-$(CH_2)_5$-		H	H	
102	-$(CH_2)_5$-		H	H	

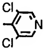
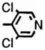
* In the Table, Me represents CH_3 and Et represents C_2H_5, respectively.

Table 4 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	R^5
103	H	H	H	Me	
104	H	H	H	Me	
105	H	$-(CH_2)_4-$		H	
106	CN	single bond		H	
107	COC_6H_5	single bond		H	
108	COC_6H_5	single bond		H	
109	n-Bu	single bond		H	
110	i-Bu	single bond		H	
111	Ph	single bond		H	
112		single bond		H	
113		single bond		H	

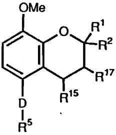
* In the Table, Me represents CH_3, Et represents C_2H_5, n-Bu represents $(CH_2)_3CH_3$, i-Bu represents $(CH_3)_2CHCH_2$, and Ph represents C_6H_5, respectively.

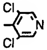
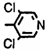
Table 4 (continued)

Compd. No.	R^1	R^2	R^{13}	R^{12}	R^5
114		single bond		H	
115		single bond		H	
116		single bond		H	
117		single bond		H	
118	H	single bond		Ph	
119	H	single bond		CH_2CO_2Et	
120	H	single bond		CH_2CO_2Et	

* In the Table, Et represents C_2H_5 and Ph represents C_6H_5, respectively.

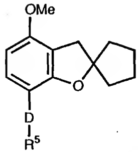
Table 5

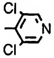
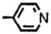
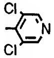
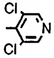
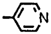


Compd. No.	R^1	R^2	R^{15}	R^{17}	D	R^5
121	Me	Me	single bond		CONH	
122	Me	Me	H	H	CONH	
123	$-(CH_2)_4-$		single bond		CONH	
124	$-(CH_2)_4-$		H	H	CONH	
125	$-(CH_2)_4-$		H	H	CH=CH	
126	$-(CH_2)_5-$		H	H	CH=CH	
127	$-(CH_2)_4-$		H	H	$COCH_2$	
128	$-(CH_2)_5-$		H	H	$COCH_2$	

* In the Table, Me represents CH_3.

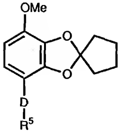
Table 6

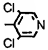
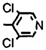
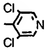


Compd. No.	D	R^5
129	CONH	
130	CONH	
131	CH=CH	
132	$COCH_2$	
133	$COCH_2$	

* In the Table, Me represents CH_3.

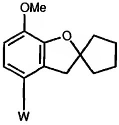
Table 7

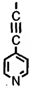
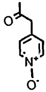
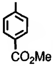
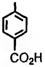
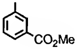
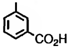


Compd. No.	D	R^5
134	CONH	
135	CONH	
136	CH_2CH_2	
137	$CHPhCH_2$	
138	CH=CH	
139	CPh=CH	
140	$COCH_2$	
141	$COCH_2$	

* In the Table, Me represents CH_3 and Ph represents C_6H_5, respectively.

Table 8



Compd. No.	W
142	
143	
144	
145	
146	
147	

* In the Table, Me represents CH_3.

The pharmacological activities of the representative Compounds (I) are described in more detail by Test Examples.

Test Example 1 Inhibition of the PDE IV Enzyme derived from a Dog Trachea

cAMP-specific phosphodiesterase (PDE IV) was purified from a dog tracheal smooth muscle according to the method of Torphy et al. [Molecular Pharmacol., 37, 206-214 (1990)]. The PDE activity was measured by the following two steps according to the method of Kincaid and Manganiello et al. [Method in Enzymology (J. D. Corbin and R. A. Jonson, Eds.), 199, 457-470 (1988)]. Using [^{3}H]cAMP (at a final concentration of 1 μM) as a substrate, the reaction was carried out in a standard mixture containing N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (50 mM, pH=7.2), $MgCl_2$ (1 mM), and soybean trypsin inhibitor (0.1 mg/ml). The reaction was initiated by adding the enzyme, followed by incubation at 30°C for 10 to 30 minutes. After stopping the reaction with hydrochloric acid, the generated 5'-AMP was completely decomposed by 5'-nucleotidase.

The resultant was subjected to chromatography on DEAE-Sephadex A-25, and radio activity of the eluted [^{3}H] adenosine was counted using a scintillation counter. Each of the test drugs was dissolved in DMSO (final concentration 1.7%) and then added to the mixture.

The results are shown in Table 9.

Table 9

Compound No.	Enzyme Inhibitory Activity (%, 10^{-6}M)
2	77
3	75
4	53
5	85
6	66
7	37
8	5
9	22
11	6
12	8
13	91
15	75
16	24
17	63
18	79
19	87
20	80
21	84
22	85
24	80
25	85
26	79
27	75
28	83
29	85
30	85
31	89
32	81
33	71
34	100
36	87
38	89
39	77

Table 9 (continued)

Compound No.	Enzyme Inhibitory Activity (%, 10^{-6}M)
40	89
41	58
42	63
43	62
45	74
47	68
48	41
49	40
50	69
51	67
52	86
53	84
54	81
55	86
59	24
60A	15
60B	4
62	45
63	85
64	78
65	74
66	49
68	80
70	68
71	87
74	73
75	72
76	93
77	87
79	45
80	17
81	69
83	85

Table 9 (continued)

Compound No.	Enzyme Inhibitory Activity (%, 10^{-6}M)
84	87
85	87
87	61
89	33
93	23
97	92
98	85
99	91
100	99
102	95
103	48
104	88
105	66
107	63
109	79
110	80
111	69
114	90
115	89
117	69
118	80
121	85
122	92
124	57
125	71
126	68
127	71
128	62
131	51
132	66
136	71
137	61
139	54
142	76

Test Example 2 Suppression of Passive Suhults-Dale Response in Guinea Pig Bronchial Smooth Muscle

For passive sensitization, rabbit anti-ovalbumin serum prepared by the method of Kohda et al. [Nichiyakurishi, 66, 237 (1970)] was peritoneally administered to male Hartley guinea pigs weighing 350 to 500 g, and 24 hours later the tracheae thereof were removed to be used for the experiment. Zig-zag strips were prepared from the tracheae in accordance with the method of Emmerson and Mackay [J. Pharm. Pharmacol., 31, 798 (1979)], and they were suspended in a Krebs-Henseleit solution with aeration of a mixture of 95% oxygen and 5% carbon dioxide at 37°C. After stabilizing for approximately one hour, ovalbumin, as the antigen, was added to the mixture (at a final concentration of 1 µm/ml), and the constriction of the muscle was recorded by a recorder (TYPE 3066; Yokokawa Hokushin Denki) via an isotonic transducer (TD-112S; Nippon Koden). A test compound was cumulatively added to the mixture after the constriction had reached the plateau, and the relaxation ratio was determined. The concentration (IC_{50}) causing 50% relaxation was calculated by linear regression analysis. The IC_{50} value of Compound 68 of the present invention was 1.6 µM.

Test Example 3 Suppression of Histamine-Induced Bronchoconstriction Response in Guinea Pig

This test was carried out by a modified Konzett and Rössler method. Under anesthesia with urethane (1.2 g/kg, ip), male Hartley guinea pigs (body weight: 500 to 600 g) were fixed on plates by strings. After undertaking a tracheotomy, cannulae were inserted to the tracheae, right carotid arteries, and left cervical veins. The spontaneous respiration of the guinea pigs was stopped by the administration of gallamie (10 mg/kg) from the left cervical veins via the cannulae. The cannulae inserted into the tracheae were connected to a bronchospasm transducer (Ugo Basile) and a respirator (TB-101, Takashima-shoten, 60 to 70 strokes/minutes, output: 5 cc) and the air overflow volume was recorded by a polygraph (RM-45, Nippon Koden) to measure the amount of bronchoconstriction. For measuring blood pressure, the cannulae inserted in the right carotid arteries were connected to a blood-pressure transducer. Constant bronchoconstriction occurred when histamine (10 µM/kg, iv) was administered at 3 minutes intervals, and the induced bronchoconstriction was used as the control. A test compound was intravenously administered, and one minute later histamine (0.3 mg/kg, iv) was administered. The test compound was cumulatively administered at 5 minutes intervals, and the bronchoconstriction in control and that after the administration of the test compound was compared.

In this test, the ED_{50} value (50% effective dose) of Compound 68 was 0.076 mg/kg in the case of intravenous administration.

Test Example 4 Effect on Anaphylactic Bronchoconstriction Response

For passive sensitization, 1 ml of rabbit anti-ovalbumine serum was peritoneally administered to male Hartley guinea pigs, and 16 to 24 hours later, ovalbumine was intravenously administered as the antigen. The induced anaphylactic bronchoconstriction was measured by the modified Konzett and Rössler method. Each of the tracheal cannulae was completely closed at the end of the measurement and the measured constriction was defined as the maximum constriction. Changes in the constriction were measured as percentage in the maximum constriction. The area under the curve (AUC) indicating the strength of the response was calculated by an image analyzer (MCID system, Imaging Research Company). The test compound was orally administered one hour before the antigen administration, and the ED_{50} value of each drug was calculated from the AUC suppression ratio by linear regression analysis.

In this test, the ED_{50} value (50% effective dose) of Compound 100 was 0.53 mg/kg by oral administration.

Although Compound (I) or pharmaceutically acceptable salts thereof may be administered as they are, it is usually desirable to provide them in the form of various pharmaceutical preparations. Such pharmaceutical preparations may be used for animals and human beings.

The pharmaceutical preparations in accordance with the present invention may contain Compound (I) or a pharmaceutically acceptable salt thereof, as an active ingredient, either solely or as a mixture with other therapeutically effective components. The pharmaceutical preparations may be prepared by any means which are well known in the technical field of pharmaceutics after mixing the active ingredient with one or more pharmaceutically acceptable carriers.

It is desired to use the administration route which is the most effective in therapy such as oral route or parenteral route which includes intrabuccal, intratracheal, intrarectal, subcutaneous, intramuscular, and intravenous administrations.

Examples of the dosage form are nebulae, capsules, tablets, granules, syrups, emulsions, suppositories, injections, ointments, and tapes.

Liquid preparations suitable for oral administration such as emulsions and syrups can be prepared using water; sugars such as sucrose, sorbitol, and fructose; glycols such as polyethylene glycol and propylene glycol; oils such as sesame oil, olive oil, and soybean oil; preservatives such as p-hydroxybenzoate; flavors such as strawberry and peppermint; and the like. Capsules, tablets, powders, granules, and the like can be prepared using excipients such as lac-

tose, glucose, sucrose, and mannitol; disintegrators such as starch and sodium alginate; lubricants such as magnesium stearate and talc; binders such as polyvinyl alcohol, hydroxypropyl cellulose, and gelatin; surfactants such as fatty acid esters; plasticizers such as glycerin; and the like.

Preparations suitable for parenteral administration comprise sterilized aqueous preparations of the active compound which are preferably isotonic to the blood of the patient. For example, a solution for injection is prepared using a carrier such as a salt solution, a glucose solution, or a mixture of a salt solution and a glucose solution. Preparations for intrarectal administration are prepared using a carrier such as cacao fat, hydrogenated fat, or a hydrogenated carboxylic acid, and provided as suppositories. Nebulae are prepared using an active compound per se or with carriers which can disperse the active compound as fine particles to facilitate absorption without stimulating oral or respiratory mucosa. Practical examples of the carrier are lactose and glycerin. Preparations such as aerosols and dry powders can be used depending upon the properties of the active compound and the employed carriers.

These parenteral preparations may also contain one or more auxiliary components selected from diluents, flavors, preservatives, excipients, disintegrators, lubricants, binders, surfactants, and plasticizers, all of which are mentioned in the above oral preparations.

The effective dose and the administration schedule of Compounds (I) or pharmaceutically acceptable salts thereof may vary depending upon the administration route, age and body weight of a patient, and the type or degree of the disease to be treated, but usually, in the case of oral administration, the effective compound is administered in a dose of 0.01 mg to 1 g, preferably, 0.05 to 50 mg/person/day at one time or in several parts. In the case of parenteral administration such as intravenous injection, the effective compound is administered in a dose of 0.001 to 100 mg, preferably, 0.01 to 10 mg/person/day at one time or in several parts. These doses should, however, vary depending upon various conditions as given above.

Certain embodiments of the present invention are illustrated in the following examples and reference examples.

Best Mode for Carrying Out the Invention

Example 1

4-(3,5-Dichloro-4-pyridylaminocarbonyl)-7-methoxy-2,3-dihydrobenzofuran (Compound 1)

A mixture of Compound IIw (0.61 g) obtained in Reference Example 23, thionyl chloride (3.6 ml), and dichloromethane (3.6 ml) was heated under reflux for 40 minutes. After being allowed to stand for cooling, the solvent was distilled off and the residue was dissolved in dry toluene. The sovent was distilled off under reduced pressure for removal of the residual thionyl chloride to give a crude acid chloride.

4-Amino-3,5-dichloropyridine (0.73 g) was dissolved in THF (7 ml) and sodium hydride (360 mg) was added thereto under ice-cooling, followed by stirring at room temperature for 15 minutes, and then the mixture was again cooled with ice. A solution of the crude acid chloride obtained above in THF (5 ml) was dropwise added to the mixture under ice-cooling, followed by stirring for one hour under ice-cooling. The reaction mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was recrystallized from ethyl acetate to give Compound 1 (0.60 g, 48.0%) as a white solid.

Melting point: 196-197 °C
NMR(DMSO-d_6, δ, ppm): 3.43(t, J=9.3Hz, 2H), 3.86(s, 3H), 4.57(t, J=9.3Hz, 2H), 7.00(d, J=8.8Hz, 1H), 7.49(d, J=8.8Hz, 1H), 8.72(s, 2H), 10.3(s, 1H)
MASS(m/e): 338(M^+)
IR(KBr, cm^{-1}): 1650, 1490, 1280

Elemental analysis: $C_{15}H_{12}N_2O_3Cl_2$			
Found (%)	C:53.14,	H:3.50,	N:8.06
Calcd.(%)	C:53.12,	H:3.57,	N:8.26

Example 2

(±)-4-(3,5-Dichloro-4-pyridylaminocarbonyl)-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound 2)

Substantially the same procedure as in Example 1 was repeated using Compound IIx (0.116 g) obtained in Reference Example 24 to give Compound 2 (0.145 g, 74%) as a white solid.

Melting point: 198-200 °C (solidified by water)
NMR($CDCl_3$, δ, ppm): 1.32(d, J=8.4Hz, 3H), 3.96(s, 3H), 3.98-4.12(m, 1H), 4.38(dd, J=9.3, 3.4Hz, 1H), 4.62-4.77(m, 1H), 6.84(d, J=9.7Hz, 1H), 7.35(d, J=9.7Hz, 1H), 7.57-7.68(brs, 1H), 8.57(s, 2H)
IR(KBr, cm^{-1}): 1670, 1490, 1283
MASS(m/z): 353(M^+)

Elemental analysis: $C_{16}H_{14}Cl_2N_2O_3$			
Found (%)	C:54.53,	H:3.89,	N:7.83
Calcd.(%)	C:54.41,	H:4.00,	N:7.93

Example 3

(±)-4-(3,5-Dichloro-4-pyridylaminocarbonyl)-3-ethyl-7-methoxy-2,3-dihydrobenzofuran (Compound 3)

Substantially the same procedure as in Example 1 was repeated using Compound IIy (0.222 g) obtained in Reference Example 25 to give Compound 3 (0.170 g, 46.3%) as a white solid.

Melting point: 202-204 °C (ethanol)
NMR($CDCl_3$, δ, ppm): 0.91(t, J=8.0Hz, 3H), 1.47-1.88 (m, 2H), 3.85-4.05(m, 1H), 3.95(s, 3H), 4.47-4.72(m, 2H), 6.85(d, J=9.7Hz, 1H), 7.35(d, J=9.7Hz, 1H), 7.50-7.69(brs, 1H), 8.59(s, 2H)
IR(KBr, cm^{-1}): 1668, 1488, 1280
MASS(m/z): 367(M^+)

Elemental analysis: $C_{17}H_{16}Cl_2N_2O_3$			
Found (%)	C:55.58,	H:4.34,	N:7.56
Calcd.(%)	C:55.60,	H:4.39,	N:7.63

Example 4

(±)-4-(3,5-Dichloro-4-pyridylaminocarbonyl)-7-methoxy-3-(2-propyl)-2,3-dihydrobenzofuran (Compound 4)

Substantially the same procedure as in Example 1 was repeated using Compound IIz (0.160 g) obtained in Reference Example 26 to give Compound 4 (0.15 g, 58%) as a white solid.

Melting point: 239-241 °C
NMR(DMSO-d_6, δ, ppm): 0.60(d, J=7.5Hz, 3H), 0.89(d, J=7.1Hz, 3H), 1.98-2.15(m, 1H), 3.80-3.91(m, 1H), 3.85(s, 3H), 4.36-4.60(m, 2H), 7.01(d, J=9.4Hz, 1H), 7.40(d, J=9.4Hz, 1H), 8.75(s, 2H), 10.48(s, 1H)
IR(KBr, cm^{-1}): 1650, 1490, 1280
MASS(m/z): 381(M^+)

Elemental analysis: $C_{18}H_{18}Cl_2N_2O_3$			
Found (%)	C:56.56,	H:4.80,	N:7.26
Calcd.(%)	C:56.71,	H:4.76,	N:7.35

Example 5

(±)-4-(3,5-Dichloro-4-pyridylaminocarbonyl)-3-ethoxycarbonylmethyl-7-methoxy-2,3-dihydrobenzofuran (Compound 5)

Substantially the same procedure as in Example 1 was repeated using Compound IIaa (0.172 g) obtained in Reference Example 27 to give Compound 5 (0.131 g, 52%) as a white solid.

Melting point: 186-188 °C (ethanol)
NMR($CDCl_3$, δ, ppm): 1.22(t, J=7.6Hz, 3H), 2.52(dd, J=16.9, 11.8Hz, 1H), 2.94-3.12(m, 1H), 3.97(s, 3H), 4.11(q, J=7.6Hz, 2H), 4.24-4.41(m, 1H), 4.59(dd, J=10.1, 4.2Hz, 1H), 4.70-4.83(m, 1H), 6.88(d, J=9.3Hz, 1H), 7.37(d, J=9.3Hz, 1H), 7.58-7.72(brs, 1H), 8.58(s, 2H)
IR(KBr, cm^{-1}): 1722, 1662, 1493, 1285
MASS(m/z): 425(M^+)

Elemental analysis: $C_{19}H_{18}Cl_2N_2O_5$			
Found (%)	C:53.65,	H:4.11,	N:6.59
Calcd.(%)	C:53.66,	H:4.27,	N:6.59

Example 6

(±)-3-Ethoxycarbonylmethyl-7-methoxy-4-pyridylaminocarbonyl-2,3-dihydrobenzofuran (Compound 6)

Substantially the same procedure as in Example 1 was repeated using 4-aminopyridine instead of 4-amino-3,5-dichloropyridine and using Compound IIaa (4.00 g) obtained in Reference Example 27 to give Compound 6 (4.77 g, 94%) as white crystals.

Melting point: 177 °C
NMR(DMSO-d_6, δ, ppm): 1.14(t, 3H, J=7Hz), 2.56-2.46 (m, 1H), 2.79(dd, 1H, J=3Hz, 16Hz), 3.88(s, 3H), 4.04(q, 2H, J=7Hz), 4.36-4.16(m, 1H)4.47(dd, 1H, J=4Hz, 9Hz), 4.64(t, 1H, J=9Hz), 7.08(d, 1H, J=9Hz), 7.65(d, 1H, J=9Hz), 8.35(d, 2H, J=8Hz), 8.74(d, 2H, J=7Hz), 11.64(s, 1H)
IR(KBr, cm^{-1}): 1697, 1614, 1506, 1471, 1269
MASS(m/e): 401(M^+)

Elemental analysis: $C_{19}H_{20}N_2O_5 \cdot 1HCl \cdot 0.5H_2O$			
Found (%)	C:56.79,	H:5.52,	N:6.97
Calcd. (%)	C:57.05,	H:5.50,	N:6.99

Example 7

(±)-3-Ethoxycarbonylmethyl-7-methoxy-4-phenylaminocarbonyl-2,3-dihydrobenzofuran (Compound 7)

Substantially the same procedure as in Example 1 was repeated using aniline instead of 4-amino-3,5-dichloropyridine and using Compound IIaa (0.50 g) obtained in Reference Example 27 to give Compound 7 (0.59 g, 92%) as a white solid.

Melting point: 169-170 °C
NMR($CDCl_3$, δ, ppm): 2.22(t, 3H, J=7Hz), 2.51(dd, 1H, J=11Hz, 17Hz), 3.08(dd, 1H, J=3Hz, 17Hz), 3.93(s, 3H), 4.11(q, 2H, J=7Hz), 4.39-4.29(m, 1H), 4.55 (dd, 1H, J=3Hz, 9Hz), 4.75(t, 1H, J=9Hz), 6.82(d, 1H, J=9Hz), 7.20-7.12 (m, 3H), 7.36(d, 1H, J=9Hz), 7.40(s, 1H), 7.58(d, 2H, J=8Hz), 7.72(s, 1H)
IR(KBr, cm^{-1}): 3305, 1722, 1645, 1286, 1194
MASS(m/e): 355(M^+)

Elemental analysis: $C_{20}H_{21}NO_5$			
Found (%)	C:67.59,	H:5.96,	N:3.94
Calcd. (%)	C:67.72,	H:5.98,	N:3.95

Example 8

(±)-4-Cyclohexylaminocarbonyl-3-ethoxycarbonylmethyl-7-methoxy-2,3-dihydrobenzofuran (Compound 8)

Substantially the same procedure as in Example 1 was repeated using cyclohexylamine instead of 4-amino-3,5-dichloropyridine and using Compound IIaa (0.60 g) obtained in Reference Example 27 to give Compound 8 (0.68 g, 87%) as a white solid.

Melting point: 197-199 °C
NMR($CDCl_3$, δ, ppm): 1.24(t, 3H, J=7Hz), 1.49-1.29(m, 5H), 2.17-2.00(m, 5H), 2.47(dd, 1H, J=11Hz, 17Hz), 3.07(dd, 1H, J=3Hz, 17Hz), 3.90(s, 3H), 4.13(q, 2H, J=7Hz), 4.31-4.23(m, 1H), 4.53(dd, 1H, J=3Hz, 9Hz), 4.72(t, 1H, J=9Hz), 5.87 (d, 1H, J=8Hz), 6.75(d, 1H, J=8Hz), 7.01(d, 1H, J=8Hz), 7.27(s, 1H)
IR(KBr, cm^{-1}): 3284, 1726, 1718, 1624, 1541, 1524, 1284
MASS(m/e): 361(M^+)

Elemental analysis: $C_{20}H_{27}NO_5$			
Found (%)	C:66.46,	H:7.53,	N:3.88
Calcd. (%)	C:66.38,	H:7.75,	N:4.00

Example 9

(±)-3-Carboxymethyl-4-(3,5-dichloro-4-pyridylaminocarbonyl)-7-methoxy-2,3-dihydrobenzofuran (Compound 9)

Compound 5 (0.329 g) obtained in Example 5 was mixed with a 2N aqueous solution of sodium hydroxide (6.6 ml), followed by stirring at room temperature for one hour. Under ice-cooling, the reaction mixture was adjusted to pH 2 by adding hydrochloric acid, and then the precipitated solid was collected by filtration. The obtained crude product was recrystallized from ethanol to give Compound 9 (0.302 g, 98%) as a white solid.

Melting point: 259-263 °C
NMR(DMSO-d_6, δ, ppm): 2.40(dd, J=14.5, 8.9Hz, 1H), 2.70-2.89(m, 1H), 3.86(s, 3H), 4.03-4.21(m, 1H), 4.34-

4.49(m, 1H), 4.55-4.74(m, 1H), 7.04(d, J=8.4Hz, 1H), 7.49(d, J=8.4Hz, 1H), 8.75(s, 2H), 10.51(s, 1H), 12.17-12.49(brs, 1H)
IR(KBr, cm^{-1}): 1713, 1663, 1490, 1288
MASS(m/z): 397(M^+)

Elemental analysis: $C_{17}H_{14}Cl_2N_2O_5 \cdot 0.5C_2H_6O \cdot 0.5H_2O$			
Found (%)	C:50.49,	H:4.37,	N:6.31
Calcd.(%)	C:50.37,	H:4.23,	N:6.53

Example 10

(±)-3-Carboxymethyl-7-methoxy-4-pyridylaminocarbonyl-2,3-dihydrobenzofuran (Compound 10)

Substantially the same procedure as in Example 9 was repeated using Compound 6 (4.00 g) obtained in Example 6 to give Compound 10 (2.79 g, 76%) as a white solid.

Melting point: 227-233 °C
NMR(DMSO-d_6, δ, ppm): 2.41(dd, 1H, J=6Hz, 17Hz), 2.72(dd, 1H, J=3Hz, 17Hz), 3.88(s, 3H), 4.20-4.10(m, 1H), 4.45(dd, 1H, J=4Hz, 9Hz), 4.64(t, 1H, J=9Hz), 7.08(d, 1H, J=9Hz), 7.42(d, 1H, J=9Hz), 8.30(d, 2H, J=7Hz), 8.72(d, 2H, J=7Hz), 11.53(s, 1H), 12.35(brs, 1H)
IR(KBr, cm^{-1}): 3300(br), 2770(br), 1716, 1693, 1614, 1508, 1477, 1271
MASS(m/e): 390(M^+)

Elemental analysis: $C_{17}H_{16}N_2O_5 \cdot HCl \cdot 0.2C_2H_6O \cdot H_2O$			
Found (%)	C:53.56,	H:5.17,	N:7.18
Calcd.(%)	C:53.63,	H:5.11,	N:7.11

Example 11

(±)-3-Carboxymethyl-7-methoxy-4-phenylaminocarbonyl-2,3-dihydrobenzofuran (Compound 11)

Substantially the same procedure as in Example 9 was repeated using Compound 7 (0.43 g) obtained in Example 7 to give Compound 11 (0.37 g, 94%) as a white solid.

Melting point: 248-251 °C
NMR(DMSO-d_6, δ, ppm): 2.38(dd, 1H, J=11Hz, 17Hz), 2.78(dd, 1H, J=2Hz, 17Hz), 3.84(s, 3H), 4.18-4.11(m, 1H), 4.40(dd, 1H, J=4Hz, 9Hz), 4.64(t, 1H, J=9Hz), 6.99(d, 1H, J=8Hz), 7.09(t, 1H, J=7Hz), 7.36-7.30(m, 3H), 7.72(d, 2H, J=8Hz), 10.15(s, 1H), 12.31(brs, 1H)
IR(KBr, cm^{-1}): 2900(br), 1709, 1645, 1595, 1506, 1442, 1286
MASS(m/e): 327(M^+)

Elemental analysis: $C_{18}H_{17}NO_5$			
Found (%)	C:66.05,	H:5.23,	N:4.28
Calcd.(%)	C:65.82,	H:5.20,	N:4.22

Example 12

(±)-3-Carboxymethyl-4-cyclohexylaminocarbonyl-7-methoxy-2,3-dihydrobenzofuran (Compound 12)

Substantially the same procedure as in Example 9 was repeated using Compound 8 (0.47 g) obtained in Example 8 to give Compound 12 (0.40 g, 95%) as a white solid.

Melting point: 246-247 °C
NMR(DMSO-d_6, δ, ppm): 1.36-1.06(m, 5H), 1.80-1.53(m, 5H), 2.31(dd, 1H, J=11Hz, 17Hz), 2.76(dd, 1H, J=2Hz, 17Hz), 3.75-3.69(m, 1H), 3.80(s, 3H), 4.13-4.06(m, 1H), 4.36(dd, 1H, J=4Hz, 9Hz), 4.59 (t, 1H, J=9Hz), 6.89(d, 1H, J=9Hz), 7.13(d, 1H, J=9Hz), 8.06(d, 1H, J=8Hz), 12.31(brs, 1H).
IR(KBr, cm^{-1}): 3410, 3134(br), 1727, 1546, 1282
MASS(m/e): 333(M^++1)

Elemental analysis: $C_{18}H_{23}NO_5$			
Found (%)	C:64.85,	H:6.95,	N:4.20
Calcd.(%)	C:64.99,	H:7.08,	N:4.28

Example 13

(±)-3-Benzyloxycarbonylmethyl-4-(3,5-dichloro-4-pyridylaminocarbonyl)-7-methoxy-2,3-dihydrobenzofuran (Compound 13)

Compound 9 (0.291 g) obtained in Example 9 was dissolved in dichloromethane (2.9 ml) and thionyl chloride (1.5 ml) was added thereto, followed by stirring at room temperature for one hour. The solvent was distilled off under reduced pressure, the residue was again dissolved in toluene, and the solvent was distilled off under reduced pressure. Benzyl alcohol (2 ml) was added to the residue followed by heating under reflux for 30 minutes. The reaction solution was concentrated and the residue was recrystallized from ethanol to give Compound 13 (0.304 g, 85.2%) as a white solid.

Melting point: 198-205 °C
NMR(DMSO-d_6, δ, ppm): 2.43-2.68(m, 1H), 2.80-3.01(m, 1H), 3.85(s, 3H), 4.10-4.27(m, 1H), 4.39-4.75(m, 2H), 5.08(s, 2H), 7.05(d, J=9.5Hz, 1H), 7.24-7.43(m, 5H), 7.50(d, J=9.5Hz, 1H), 8.77(s, 2H), 10.50(s, 1H)
IR(KBr, cm^{-1}): 1722, 1668, 1490, 1288
MASS(m/z): 487(M^+)

Elemental analysis: $C_{24}H_{20}Cl_2N_2O_5$			
Found (%)	C:59.32,	H:4.00,	N:5.72
Calcd.(%)	C:59.15,	H:4.14,	N:5.75

Example 14

(±)-3-Benzyloxycarbonylmethyl-7-methoxy-4-pyridylaminocarbonyl-2,3-dihydrobenzofuran (Compound 14)

Substantially the same procedure as in Example 13 was repeated using Compound 10 (0.12 g) obtained in Example 10 to give Compound 14 (0.07 g, 53%) as a white solid.

Melting point: 165-166 °C

NMR($CDCl_3$, δ, ppm): 2.60(dd, 1H, J=10Hz, 17Hz), 3.06 (dd, 1H, J=3Hz, 17Hz), 3.94(s, 3H), 4.40-4.33(m, 1H), 4.57(dd, 1H, J=4Hz, 10Hz), 4.74(t, 1H, J=9Hz), 5.10(s, 2H), 6.82(d, 1H, J=9Hz), 7.16(d, 2H, J=9Hz), 7.38-7.28(m, 5H), 7.52(dd, 1H, J=1Hz, 5Hz), 7.77(brs, 1H), 8.53(dd, 2H, J=1Hz, 5Hz)
IR(KBr, cm^{-1}): 3317, 1720, 1653, 1585, 1504, 1284
MASS(m/e): 418(M^+)

Elemental analysis: $C_{24}H_{22}N_2O_5 \cdot 0.1C_2H_6O \cdot 0.4H_2O$			
Found (%)	C:67.56,	H:5.48,	N:6.51
Calcd.(%)	C:67.54,	H:5.40,	N:6.47

Example 15

(±)-3-Benzyloxycarbonylmethyl-7-methoxy-4-phenylaminocarbonyl-2,3-dihydrobenzofuran (Compound 15)

Substantially the same procedure as in Example 13 was repeated using Compound 11 (0.17 g) obtained in Example 11 to give Compound 15 (0.17 g, 76%) as a white solid.

Melting point: 179-180 °C
NMR($CDCl_3$, δ, ppm): 2.59(dd, 1H, J=11Hz, 17Hz), 3.13 (dd, 1H, J=3Hz, 17Hz), 3.93(s, 3H), 4.42-4.32(m, 1H), 4.55(dd, 1H, J=4Hz, 9Hz), 4.74(t, 1H, J=9Hz), 5.08(d, 1H, J=3Hz), 6.81(d, 1H, J=9Hz), 7.16(d, 1H, J=9Hz), 7.39-7.26(m, 8H), 7.55(dd, 2H, J=1Hz, 8Hz), 7.66(s, 1H)
IR(KBr, cm^{-1}): 3307, 1722, 1645, 1529, 1506, 1444, 1288
MASS(m/e): 417(M^+)

Elemental analysis: $C_{25}H_{23}NO_5$			
Found (%)	C:71.93,	H:5.55,	N:3.36
Calcd.(%)	C:71.82,	H:5.51,	N:3.36

Example 16

(±)-3-Benzyloxycarbonyl-4-cyclohexylaminocarbonyl-7-methoxy-2,3-dihydrobenzofuran (Compound 16)

Substantially the same procedure as in Example 13 was repeated using Compound 12 (0.20 g) obtained in Example 12 to give Compound 16 (0.20 g, 76%) as a white solid.

Melting point: 178-179 °C
NMR(DMSO-d_6, δ, ppm): 1.34-1.00(m, 5H), 1.86-1.66(m, 5H), 2.56-2.46(m, 1H), 2.88(dd, 1H, J=3Hz, 17Hz), 3.76-3.62(m, 1H), 3.80(s, 3H), 4.19-4.12(m, 1H), 4.37(dd, 1H, J=4Hz, 9Hz), 4.58(t, 1H, J=9Hz), 5.10(d, 1H, J=2Hz), 6.90(d, 1H, J=9Hz), 7.15(d, 1H, J=9Hz), 7.41-7.31(m, 5H), 8.06(d, 1H, J=8Hz)
IR(KBr, cm^{-1}): 3325, 1720, 1626, 1282, 1174
MASS(m/e): 423(M^+)

Elemental analysis: $C_{25}H_{29}NO_5$			
Found (%)	C:70.90,	H:6.90,	N:3.30
Calcd.(%)	C:70.90,	H:7.04,	N:3.34

Example 17

(±)-4-(3,5-Dichloro-4-pyridylaminocarbonyl)-7-methoxy-3-(4-methylpiperazine-1-ylcarbonylmethyl)-2,3-dihydrobenzofuran • hydrochloride (Compound 17)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.354 g) obtained in Example 9 and N-methylpiperazine (0.119 ml) to give (±)-4-(3,5-dichloro-4-pyridylaminocarbonyl)-7-methoxy-3-(4-methylpiperazin-1-ylcarbonylmethyl)-2,3-dihydrobenzofuran (0.427 g, 100%) as an oily substance. The obtained free base was dissolved in ethyl acetate (50 ml), and a saturated solution of hydrochloric acid in ethyl acetate (2 ml) was added thereto followed by stirring. The precipitated hydrochloride was collected by filtration and washed with ethyl acetate to give Compound 17 as a white solid.

Melting point: 181-187 °C
NMR(DMSO-d_6, δ, ppm): 2.40-3.52(m, 13H), 3.77-4.70(m, 3H), 3.88(s, 3H), 7.06(d, J=9.6Hz, 1H), 7.52(d, J=9.6Hz, 1H), 8.76(s, 2H), 10.55(s, 1H)
IR(KBr, cm^{-1}): 1650, 1480, 1280

Elemental analysis: $C_{22}H_{24}Cl_2N_4O_4 \cdot HCl \cdot 2.5H_2O$			
Found (%)	C:47.08,	H:5.29,	N:9.94
Calcd.(%)	C:47.11,	H:5.39,	N:9.99

Example 18

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-[(3-pyridylmethyl)aminocarbonyl]methyl-2,3-dihydrobenzofuran (Compound 18)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.30 g) obtained in Example 9 and 3-pyridylmethylamine to give Compound 18 (0.07 g, 19%) as a white solid.

Melting point: 258-261 °C (decomposed)
NMR($CDCl_3$, δ, ppm): 2.46(dd, 1H, J=10Hz, 14 Hz), 2.82 (dd, 1H, J=2Hz, 14Hz), 3.95(s, 3H), 4.24-4.15(m, 1H), 4.32(dd, 1H, J=6Hz, 15Hz), 4.46, 4.32(dd, 1H, J=6Hz, 15Hz), 4.67(t, 1H, J=9Hz), 4.83(dd, 1H, J=3Hz, 9Hz), 6.65-6.55(m, 1H), 6.85(d, J=8Hz, 1H), 7.26-7.21(m, 1H), 7.37(d, J=8Hz, 1H), 7.65-7.55(m, 1H), 8.57-8.38(m, 2H), 8.56(s, 2H)
IR(KBr, cm^{-1}): 3310, 3224, 1662, 1645, 1489, 1284
MASS(m/e): 486(M^+-1)

Example 19

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-[(3-pyridyl)aminocarbonyl]methyl-2,3-dihydrobenzofuran (Compound 19)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.30 g) obtained in Example 9 and 3-aminopyridine to give Compound 19 (0.18 g, 51%) as a white solid.

Melting point: 267 °C (decomposed)
NMR($CDCl_3$, δ, ppm): 2.55(dd, 1H, J=11Hz, 15 Hz), 3.01 (dd, 1H, J=2Hz, 15Hz), 3.94(s, 3H), 4.30-4.21(m, 1H), 4.67(t, 1H, J=9Hz), 4.80(dd, 1H, J=3Hz, 9Hz), 6.87(d, 1H, J=9Hz), 7.24(dd, 1H, J=5Hz, 8Hz), 7.45(d, 1H, J=9Hz), 8.22-8.10(m, 2H), 8.50 (d, 1H, J=2Hz), 8.56(s, 2H)
IR(KBr, cm^{-1}): 3300(br), 1668, 1664, 1483, 1278
MASS(m/e): 472(M^+-1)

Example 20

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-[(2-pyrimidyl)aminocarbonyl]methyl-2,3-dihydrobenzofuran (Compound 20)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.30 g) obtained in Example 9 and 2-aminopyrimidine to give Compound 19 (0.11 g, 31%) as a white solid.

Melting point: 259-261 °C
NMR(DMSO-d_6, δ, ppm): 2.82(dd, 1H, J=11Hz, 18Hz), 3.16-3.10(m, 1H), 3.87(s, 3H), 4.30-4.26(m, 1H), 4.38(dd, 1H, J=3Hz, 9Hz), 4.65(t, 1H, J=9Hz), 7.05(d, J=9Hz, 1H), 7.14(t, 1H, J=5Hz), 7.48(d, J=9Hz, 1H), 8.61(d, J=5Hz, 2H), 8.72(s, 2H), 10.49(s, 1H), 10.60(s, 1H)
IR(KBr, cm^{-1}): 3200(br), 1668, 1579, 1488, 1278
MASS(m/e): 474(M^+)

Example 21

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-[(4-phenyl-1-piperazinyl)carbonyl]methyl-2,3-dihydrobenzofuran (Compound 21)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.30 g) obtained in Example 9 and 1-phenylpiperazine to give Compound 21 (0.21 g, 51%) as a white solid.

Melting point: 224 °C
NMR($CDCl_3$, δ, ppm): 2.54(dd, 1H, J=11Hz, 16 Hz), 3.21-3.11(m, 5H), 3.75-3.57(m, 4H), 3.96(s, 3H), 4.36-4.26(m, 1H), 4.66(dd, 1H, J=3Hz, 9Hz), 4.79 (t, 1H, J=9Hz), 6.92-6.86(m, 4H), 7.31-7.25(m, 3H), 7.37(d, J=9Hz, 1H), 7.68(s, 1H), 8.57(s, 2H)
IR(KBr, cm^{-1}): 3232, 1662, 1647, 1486, 1286
MASS(m/e): 542(M^++1)

Elemental analysis: $C_{27}H_{26}N_4O_4Cl_2$			
Found (%)	C:59.83,	H:4.82,	N:10.20
Calcd.(%)	C:59.90,	H:4.84,	N:10.35

Example 22

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-[(1,2,3,4-tetrahydroisoquinolinyl)carbonyl]methyl-2,3-dihydrobenzofuran (Compound 22)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.30 g) obtained in Example 9 and 1,2,3,4-tetrahydroisoquinoline to give Compound 22 (0.32 g, 84%) as a white solid.

Melting point: 211-213 °C
NMR($CDCl_3$, δ, ppm): 2.63-2.51(m, 1H), 2.83(dt, 2H, J=6Hz, 5Hz), 3.22(d, J=16Hz, 1H), 3.92-3.60(m, 2H), 3.96(s, 3H), 4.37-4.28(m, 1H), 4.57(s, 1H), 4.82-4.61(m, 3H), 6.86(dd, 1H, J=3Hz, 9Hz), 7.23-7.10(m, 4H), 7.38(dd, 1H, J=2Hz, 9Hz), 7.76 (s, 1H), 8.56(s, 2H)
IR(KBr, cm^{-1}): 3188, 1659, 1635, 1487, 1282
MASS(m/e): 511(M^+-1)

Elemental analysis: $C_{26}H_{23}N_3O_4Cl_2$			
Found (%)	C:60.95,	H:4.52,	N:8.20
Calcd.(%)	C:60.67,	H:4.58,	N:8.00

Example 23

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-phenethyloxycarbonyl)methyl-2,3-dihydrobenzofuran (Compound 23)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.30 g) obtained in Example 9 and phenethyl alcohol to give Compound 23 (0.07 g, 57%) as a white solid.

Melting point: 194 °C
NMR($CDCl_3$, δ, ppm): 2.50(dd, 1H, J=11Hz, 17Hz), 2.90 (t, 2H, J=7Hz), 3.03(dd, 1H, J=2Hz, 17Hz), 3.95 (s, 3H), 4.27(t, 2H, J=7Hz), 4.33-4.22(m, 1H), 4.46(dd, 1H, J=3Hz, 9Hz), 4.64(t, 1H, J=9Hz), 6.86(d, 1H, J=9Hz), 7.31-7.17(m, 5H), 7.34(d, 1H, J=8Hz), 7.62(s, 1H), 8.57(s, 2H)
IR(KBr, cm^{-1}): 3203, 1726, 1660, 1487, 1286
MASS(m/e): 50 (M^++1)

Elemental analysis: $C_{25}H_{22}N_2O_5Cl_2$			
Found (%)	C:59.89,	H:4.42,	N:5.59
Calcd.(%)	C:59.75,	H:4.15,	N:5.48

Example 24

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-[(2-pyridylmethyl)aminocarbonyl]methyl-2,3-dihydrobenzofuran (Compound 24)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.30 g) obtained in Example 9 and 2-pyridylmethylamine to give Compound 24 (0.21 g, 56%) as a white solid.

Melting point: 255 -258 °C
NMR(DMSO-d_6, δ, ppm): 2.35(dd, 1H, J=11Hz, 15Hz), 2.79(dd, 1H, J=3Hz, 15Hz), 3.86(s, 3H), 4.24-4.13(m, 1H), 4.36(d, 2H, J=6Hz), 4.43-4.29(m, 1H), 4.56(t, 1H, J=9Hz), 7.04(d, 1H, J=9Hz), 7.28-7.24(m, 2H), 7.47(d, 1H, J=9Hz), 7.75(dt, 1H, J=2Hz, 8Hz), 8.51-8.43(m, 2H), 8.75(s, 2H), 10.48(s, 1H)
IR(KBr, cm^{-1}): 3350, 3320, 1659, 1635, 1552, 1486, 1282
MASS(m/e): 486(M^+)

Elemental analysis: $C_{23}H_{20}N_4O_4Cl_2$			
Found (%)	C:56.69,	H:4.14,	N:11.50
Calcd.(%)	C:56.54,	H:4.02,	N:11.33

Example 25

(±)-3-(Benzylaminocarbonyl)methyl-4-[(3,5-dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-2,3-dihydrobenzofuran (Compound 25)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.10 g) obtained in Example 9 and benzylamine to give Compound 25 (0.08 g, 65%) as a white solid.

Melting point: 284-286 °C
NMR(DMSO-d_6, δ, ppm): 2.30(dd, 1H, J=11Hz, 15Hz), 2.76(dd, 1H, J=3Hz, 15Hz), 3.86(s, 3H), 4.28-4.17(m, 1H), 4.27(d, 2H, J=7Hz), 4.34(dd, 1H, J=3Hz, 9Hz), 4.57(t, 1H, J=9Hz), 7.04(d, 1H, J=9Hz), 7.35-7.20(m, 5H), 7.47(d, 1H, J=9Hz), 8.36(t, 1H, J=6Hz), 8.75(s, 2H), 10.47(brs, 1H)
IR(KBr, cm^{-1}): 3350, 3230, 1662, 1637, 1552, 1487, 1282
MASS(m/e): 487(M^+)

Elemental analysis: $C_{24}H_{21}N_3O_4Cl_2$			
Found (%	C:59.27,	H:4.35,	N:8.64
Calcd.(%)	C:59.54,	H:4.36,	N:8.55

Example 26

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-[(4-pyridylmethyl)aminocarbonyl]methyl-2,3-dihydrobenzofuran (Compound 26)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.20 g) obtained in Example 9 and 4-pyridylmethylamine to give Compound 26 (0.04 g, 16%) as a white solid.

Melting point: 259-262 °C (decomposed)
NMR(DMSO-d_6, δ, ppm): 2.36(dd, 1H, J=11Hz, 16Hz), 2.80(dd, 1H, J=2Hz, 16Hz), 3.86(s, 3H), 4.23-4.16(m, 1H), 4.29(d, 2H, J=6Hz), 4.37(dd, 1H, J=3Hz, 9Hz), 4.57(t, 1H, J=9Hz), 7.22(d, 2H, J=9Hz), 7.47(d, 1H, J=9Hz), 8.50-8.42(m, 3H), 8.75(s, 2H), 10.48(s, 1H)
IR(KBr, cm^{-1}): 3327, 3205, 1654, 1641, 1551, 1481, 1288
MASS(m/e): 149

Elemental analysis: $C_{23}H_{20}N_4O_4Cl_2$			
Found (%)	C:56.69,	H:4.14,	N:11.50
Calcd.(%)	C:56.39,	H:4.00,	N:11.39

Example 27

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-(phenylaminocarbonyl)methyl-2,3-dihydrobenzofuran (Compound 27)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.20 g) obtained in Example 9 and aniline to give Compound 27 (0.10 g, 42%) as a white solid.

Melting point: 296-300 °C (decomposed)
NMR(DMSO-d_6, δ, ppm): 2.54-2.50(m, 1H), 2.93(dd, 1H, J=2Hz, 14Hz), 3.87(s, 3H), 4.29-4.22(m, 1H), 4.43(dd, 1H, J=3Hz, 9Hz), 4.63(t, 1H, J=9Hz), 7.07-6.98(m, 2H), 7.27(d, 1H, J=8Hz), 7.30(d, 1H, J=8Hz), 7.49(d, 1H,

J=8Hz), 7.55(d, 2H, J=8Hz), 8.74(s, 2H), 9.90(s, 1H), 10.50(s, 1H)
IR(KBr, cm^{-1}): 3350, 3142, 1657, 1651, 1547, 1491, 1290
MASS(m/e): 471(M^+-1), 473(M^++1)

Elemental analysis: $C_{23}H_{19}N_3O_4Cl_2$			
Found (%)	C:58.49,	H:4.05,	N:8.90
Calcd.(%)	C:58.14,	H:4.14,	N:8.62

Example 28

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-3-[(4-methoxybenzyl)aminocarbonyl]methyl-2,3-dihydrobenzofuran (Compound 28)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.20 g) obtained in Example 9 and 4-methoxybenzylamine to give Compound 28 (0.28 g, 85%) as a white solid.

Melting point: 269-271 °C
NMR(DMSO-d_6, δ, ppm): 2.27(dd, 1H, J=15Hz, 11Hz), 2.74(dd, 1H, J=3Hz, 15Hz), 3.72(s, 3H), 3.86(s, 3H), 4.19(d, 2H, J=5Hz), 4.23-4.12(m, 1H), 4.33 (dd, 1H, J=3Hz, 9Hz), 4.56(t, 1H, J=9Hz), 6.87(d, 2H, J=9Hz), 7.03(d, 1H, J=8Hz), 7.16(d, 1H, J=9Hz), 7.46(d, 1H, J=8Hz), 8.27(t, 1H, J=6Hz), 8.74(s, 2H), 10.47(s, 1H)
IR(KBr, cm^{-1}): 3210, 1659, 1643, 1514, 1487, 1290
MASS(m/e): 515(M^+), 517, 519

Elemental analysis: $C_{25}H_{23}N_3O_5Cl_2$			
Found (%)	C:58.15,	H:4.49,	N:8.14
Calcd.(%)	C:57.97,	H:4.51,	N:8.03

Example 29

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-3-[(4-fluorobenzyl)aminocarbonyl]methyl-7-methoxy-2,3-dihydrobenzofuran (Compound 29)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.20 g) obtained in Example 9 and 4-fluorobenzylamine to give Compound 29 (0.13 g, 51%) as a white solid.

Melting point: 287 °C
NMR(DMSO-d_6, δ, ppm): 2.28(dd, 1H, J=15Hz, 11Hz), 2.80(dd, 1H, J=3Hz, 15Hz), 3.85(s, 3H), 4.25-4.18(m, 1H), 4.23(d, 2H, J=6Hz), 4.33(dd, 1H, J=3Hz, 9Hz), 4.55(t, 1H, J=9Hz), 7.02(d, 1H, J=9Hz), 7.12(t, 2H, J=9Hz), 7.29-7.23(m, 2H), 7.45(d, 1H, J=9Hz), 8.40(t, 1H, J=6Hz), 8.73(s, 2H), 10.45(s, 1H)
IR(KBr, cm^{-1}): 3368, 3145, 1662, 1647, 1510, 1491, 1286
MASS(m/e): 63

Elemental analysis: $C_{24}H_{20}N_3O_4FCl_2$			
Found (%)	C:57.16,	H:4.00,	N:8.33
Calcd.(%)	C:57.20,	H:4.99,	N:8.33

Example 30

(±)-3-[(4-Chlorobenzyl)aminocarbonyl]methyl-4-[(3,5-dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-2,3-dihydrobenzofuran (Compound 30)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.20 g) obtained in Example 9 and 4-chlorobenzylamine to give Compound 30 (0.15 g, 58%) as a white solid.

Melting point: 283-286 °C
NMR(DMSO-d_6, δ, ppm): 2.30(dd, 1H, J=16Hz, 12Hz), 2.76(dd, 1H, J=2Hz, 16Hz), 3.34(s, 3H), 4.26-4.20(m, 1H), 4.25(d, 2H, J=6Hz), 4.34(dd, 1H, J=3Hz, 9Hz), 4.56(t, 1H, J=9Hz), 7.04(d, 1H, J=9Hz), 7.25(d, 2H, J=8Hz), 7.37(d, 2H, J=8Hz), 7.47(d, 1H, J=9Hz), 8.38(t, 1H, J=6Hz), 8.75(s, 2H), 10.48(s, 1H)
IR(KBr, cm^{-1}): 3307, 3296, 1660, 1647, 1489, 1286
MASS(m/e): 520(M^+)

Elemental analysis: $C_{24}H_{20}N_3O_4Cl_3$			
Found (%)	C:55.35,	H:3.87,	N:8.07
Calcd.(%)	C:55.22,	H:3.77,	N:7.98

Example 31

(±)-3-[(2-Chlorobenzyl)aminocarbonyl]methyl-4-[(3,5-dichloro-4-pyridyl)aminocarbonyl]-7-methoxy-2,3-dihydrobenzofuran (Compound 31)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.20 g) obtained in Example 9 and 2-chlorobenzylamine to give Compound 31 (0.15 g, 58%) as a white solid.

Melting point: 288-289 °C
NMR(DMSO-d_6, δ, ppm): 2.36(dd, 1H, J=15Hz, 12Hz), 2.80(dd, 1H, J=3Hz, 16Hz), 3.86(s, 3H), 4.22-4.17(m, 1H), 4.38-4.30(m, 3H), 4.57(t, 1H, J=9Hz), 7.39(d, 1H, J=8Hz), 7.31-7.27(m, 3H), 7.43-7.42(m, 1H), 7.47(d, 1H, J=8Hz), 8.35(brs, 1H), 8.74(s, 2H)
IR(KBr, cm^{-1}): 3350, 1660, 1651, 1547, 1493, 1286
MASS(m/e): 519(M^+-1), 521(M^++1)

Elemental analysis: $C_{24}H_{20}N_3O_4Cl_3$			
Found (%)	C:55.35,	H:3.87,	N:8.07
Calcd.(%)	C:55.42,	H:3.86,	N:8.02

Example 32

(±)-4-[(3,5-Dichloro-4-pyridyl)aminocarbonyl]-3-[(3,5-dichloro-4-pyridyl)aminocarbonyl]methyl-7-methoxy-2,3-dihydrobenzofuran (Compound 32)

Substantially the same procedure as in Example 13 was repeated using Compound 9 (0.30 g) obtained in Example 9 and 4-amino-3,5-dichloropyridine to give Compound 32 (0.06 g, 17%) as a white solid.

Melting point: >300 °C

NMR(DMSO-d_6, δ, ppm): 2.61-2.55(m, 1H), 3.07-3.01(m, 1H), 3.87(s, 3H), 4.28-4.25(m, 1H), 4.40(dd, 1H, J=2Hz, 8Hz), 4.55(t, 1H, J=8Hz), 7.07(d, 1H, J=9Hz), 7.50(d, 1H, J=9Hz), 8.68(s, 2H), 8.75(s, 2H), 10.32(brs, 2H), 10.52(brs, 2H)
IR(KBr, cm^{-1}): 3260(br), 1684, 1653, 1487, 1282
MASS(m/e): 542(M^+)

Elemental analysis: $C_{22}H_{16}N_4O_4Cl_2$			
Found (%)	C:48.73,	H:2.97,	N:10.33
Calcd.(%)	C:48.53,	H:2.91,	N:10.12

Example 33

4-(3,5-Dichloro-4-pyridylaminocarbonyl)-7-methoxybenzofuran (Compound 33)

Substantially the same procedure as in Example 1 was repeated using Compound IIac (0.22 g) obtained in Reference Example 29 to give Compound 33 (0.27 g, 68%) as a white solid.

NMR(DMSO-d_6, δ, ppm): 4.05(s, 3H), 7.10(d, J=8.7Hz, 1H), 7.31(d, J=1.5Hz, 1H), 7.99(d, J=8.7Hz, 1H), 8.10(d, J=1.5Hz, 1H), 8.77(s, 2 H), 10.5(s, 1H)
MASS(m/e): 336(M^+)
IR(KBr, cm^{-1}): 1650, 1490, 1280

Elemental analysis: $C_{15}H_{10}N_2O_3Cl_2$			
Found (%)	C:53.31,	H:2.85,	N:8.06
Calcd.(%)	C:53.44,	H:2.99,	N:8.31

Example 34

2-Cyano-4-(3,5-dichloropyridin-4-ylaminocarbonyl)-7-methoxybenzofuran (Compound 34)

Substantially the same procedure as in Example 1 was repeated using Compound IIab (0.26 g) obtained in Reference Example 28 to give Compound 34 (0.10 g, 23.9%) as a white solid.

Melting point: 246-250 °C
NMR(DMSO-d_6, δ, ppm): 4.10(s, 3H), 7.40(d, J=8.7Hz, 1H), 8.15(d, J=8.7Hz, 1H), 8.32(s, 1H), 8.79(s, 2H), 10.7(s, 1H)
IR(KBr, cm^{-1}): 2240, 1650, 1490, 1280
MASS(m/z): 362 (M^+)

Elemental analysis: $C_{16}H_9Cl_2N_3O_3$			
Found (%)	C:53.31,	H:2.30,	N:11.30
Calcd.(%)	C:53.06,	H:2.50,	N:11.60

Example 35

2-Benzoyl-4-[(3,5-dichloro-4-pyridyl)aminocarbonyl)]-7-methoxybenzofuran (Compound 35)

Compound 34 (0.46 g) obtained in Example 34 was suspended in tetrahydrofuran, 1.0M phenylmagnesium bromide (28.2 g) was dropwise added thereto under stirring at 0°C, and then the temperature of the mixture was slowly raised to room temperature while stirring for 3 hours. Hydrochloric acid was added thereto at 0°C followed by stirring for one hour. The mixture was extracted with ethyl acetate, the organic layer was washed with a saturated saline and dried over magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (toluene:ethyl acetate = 4:1) and recrystallized from ethanol to give Compound 35 (0.38 g, 67.3%) as a colorless solid.

Melting point: 217 °C
NMR(DMSO-d_6, δ, ppm): 4.11(s, 3H), 7.37(d, 1H, J=8Hz), 7.61(d, 1H, J=7Hz), 7.65(s, 1H), 7.72(d, 1H, J=7Hz), 7.97(s, 3H), 8.01(s, 3H), 8.14(d, 1H, J=8Hz), 8.76(s, 2H), 10.70(s, 1H)
IR(KBr, cm^{-1}): 3307(br), 1647, 1487, 1286, 1271
MASS(m/e): 441(M^+)

Elemental analysis: $C_{22}H_{14}N_2O_4Cl_2$			
Found (%)	C:59.88,	H:3.20,	N:6.35
Calcd.(%)	C:59.80,	H:3.18,	N:6.28

Example 36

2-Butyl-4-(3,5-dichloropyridin-4-ylaminocarbonyl)-7-methoxybenzofuran (Compound 36)

Substantially the same procedure as in Example 1 was repeated using Compound IIad (0.47 g) obtained in Reference Example 30 to give Compound 36 (0.25 g, 34%) as a white solid.

Melting point: 160-164 °C
NMR(DMSO-d_6, δ, ppm): 0.92(t, J=8Hz, 3H), 1.28-1.47(m, 2H), 1.59-1.78(m, 2H), 2.80 (t, J=7Hz, 2H), 4.01 (s, 3H), 7.00(s, 1H), 7.04(d, J=8Hz, 1H), 7.92(d, J=8Hz, 1H), 8.75(s, 2H), 10.4(s, 1H)
MASS(m/e): 392(M^+)
IR(KBr, cm^{-1}): 1658, 1490, 1285

Elemental analysis: $C_{19}H_{18}Cl_2N_2O_3$			
Found (%)	C:58.08,	H:4.68,	N:7.06
Calcd.(%)	C:58.03,	H:4.61,	N:7.12

Example 37

2-Benzyl-4-[(3,5-dichloro-4-pyridyl)aminocarbonyl]-7-methoxybenzofuran (Compound 37)

Substantially the same procedure as in Example 1 was repeated using Compound IIag (0.30 g) obtained in Reference Example 33 to give Compound 37 (0.25 g, 77%).

Melting point: 141-142 °C
NMR($CDCl_3$, δ, ppm): 4.17(s, 2H), 4.41(s, 3H), 6.43(s, 1H), 7.25(d, 1H, J=8Hz), 7.64-7.29(m, 5H), 8.07 (d, 1H, J=8Hz), 8.91(s, 2H), 9.97(brs, 1H)

IR(KBr, cm^{-1}): 3298(br), 1674, 1547, 1491, 1477, 1271
MASS(m/e): 306(M^+)

Elemental analysis: $C_{22}H_{16}N_2O_3Cl_2$			
Found (%)	C:61.84,	H:3.77,	N:6.56
Calcd.(%)	C:61.79,	H:3.75,	N:6.48

Example 38

4-(3,5-Dichloro-4-pyridylaminocarbonyl)-7-methoxy-2-(4-pyridyl)benzofuran (Compound 38)

Substantially the same procedure as in Example 1 was repeated using Compound IIae (0.21 g) obtained in Reference Example 31 to give Compound 38 (0.141 g, 50.1%) as a white solid.

Melting point: 289-290 °C
NMR(DMSO-d_6, δ, ppm): 4.10(s, 3H), 7.20(d, J=9Hz, 1H), 7.90(d, J=7Hz, 2H), 8.07(d, J=9Hz, 1H), 8.09(s, 1H), 8.69(d, J=7Hz, 2H), 8.80(s, 2H), 10.58(bs, 1H)
IR(KBr, cm^{-1}): 3300(br), 1650, 1490, 1460, 1290
MASS(m/e): 417, 415, 413(M^+), 253, 252

Elemental analysis: $C_{20}H_{13}N_3O_3Cl_2$			
Found (%)	C:57.74,	H:3.15,	N:9.91
Calcd.(%)	C:57.97,	H:3.16,	N:10.15

Example 39

7-Methoxy-2-(4-pyridyl)-4-(4-pyridylaminocarbonyl)benzofuran • 2 hydrochloride (Compound 39)

Substantially the same procedure as in Example 6 was repeated using Compound IIae (3.0 g) obtained in Reference Example 31 to give 7-methoxy-2-(4-pyridyl)-4-(4-pyridylaminocarbonyl)benzofuran (1.45 g, 42.8%) as a white solid. Then, substantially the same procedure as in Example 17 was repeated using the above-obtained product to give Compound 39.

Melting point: 214-217 °C
NMR(DMSO-d_6, δ, ppm): 4.11(s, 3H), 7.29(d, J=9Hz, 1H), 8.39(d, J=9Hz, 1H), 8.49(d, J=7Hz, 2H), 8.52(d, J=6Hz, 2H), 8.55(s, 1H), 8.80(d, J=7Hz, 2H), 8.96(d, J=6Hz, 2H), 12.05(bs, 1H)
IR(KBr, cm^{-1}): 3400(br), 1685, 1635, 1610, 1505, 1270
MASS(m/e): 345(M^+), 252

Elemental analysis: $C_{20}H_{15}N_3O_3 \cdot 2.0HCl \cdot 3.0H_2O$			
Found (%)	C:50.87,	H:4.78,	N:8.76
Calcd.(%)	C:50.86,	H:4.91,	N:8.90

Example 40

4-(3,5-Dichloro-4-pyridylaminocarbonyl)-7-methoxy-2-(2-pyridyl)benzofuran (Compound 40)

Substantially the same procedure as in Example 1 was repeated using Compound IIaf (0.40 g) obtained in Reference Example 32 to give Compound 40 (0.162 g, 29.9%) as a white solid.

Melting point: 263-264 °C
NMR(DMSO-d_6, δ, ppm): 4.12(s, 3H), 7.20(d, J=9Hz, 1H), 7.44(ddd, J=2Hz, 5Hz, 7Hz, 1H), 7.93(s, 1H), 7.97(dd, 2Hz, 8Hz, 1H), 7.99(dd, J=7Hz, 8Hz, 1H), 8.02(d, J=9Hz, 1H), 8.70(d, J=5Hz, 1H), 8.78(s, 2H), 10.55(bs, 1H)
IR(KBr, cm^{-1}): 3200(br), 1650, 1590, 1500, 1290, 1280
MASS(m/e): 417, 415, 413(M^+), 252

Elemental analysis: $C_{20}H_{13}N_3O_3Cl_2 \cdot 0.1H_2O$			
Found (%)	C:57.66,	H:3.06,	N:9.91
Calcd.(%)	C:57.74,	H:3.20,	N:10.10

Example 41

7-Methoxy-2-(2-pyridyl)-4-(4-pyridylaminocarbonyl)benzofuran • 2 hydrochloride (Compound 41)

Substantially the same procedure as in Example 6 was repeated using Compound IIaf (4.87 g) obtained in Reference Example 32 to give 7-methoxy-2-(2-pyridyl)-4-(4-pyridylaminocarbonyl)benzofuran (4.24 g, 77.1%) as a white solid. Then, substantially the same procedure as in Example 17 was repeated using the above-obtained product to give Compound 41.

Melting point: 251-254 °C
NMR(DMSO-d_6/D_2O, δ, ppm): 4.17(s, 3H), 7.13(d, J=9Hz, 1H), 7.58(dd, J=5Hz, 7Hz, 1H), 7.9-8.1(m, 2H), 7.98(s, 1H), 8.12(d, J=9Hz, 1H), 8.29(d, J=7Hz, 2H), 8.64(d, J=7Hz, 2H), 8.66(d, J=5Hz, 1H)
IR(KBr, cm^{-1}): 3400(br), 1685, 1625, 1610, 1505, 1280
MASS(m/e): 345(M^+), 252

Elemental analysis: $C_{20}H_{15}N_3O_3 \cdot 2.0HCl \cdot 1.9H_2O$			
Found (%)	C:52.99,	H:4.30,	N:9.10
Calcd.(%)	C:53.09,	H:4.63,	N:9.29

Example 42

4-(3,5-Dichloro-4-pyridylaminocarbonyl)-7-methoxy-3-phenylbenzofuran (Compound 42)

Substantially the same procedure as in Example 1 was repeated using Compound IIah (0.29 g) obtained in Reference Example 34 to give Compound 42 (0.34 g, 76%) as a white solid.

Melting point: 177-179 °C
NMR($CDCl_3$, δ, ppm): 4.12(s, 3H), 6.95(d, J=9Hz, 1H), 7.17-7.43(m, 5H), 7.76(s, 1H), 7.89(d, J=9Hz, 1H), 8.44(s, 2H)
IR(KBr, cm^{-1}): 1495, 1669, 1402, 1279
MASS(m/e): 412(M^+)

Elemental analysis: $C_{21}H_{14}N_2O_3Cl_2$			
Found (%)	C:60.99,	H:3.40,	N:6.56
Calcd.(%)	C:61.03,	H:3.41,	N:6.78

Example 43

3-Ethoxycarbonylmethyl-4-[(3,5-dichloro-4-pyridyl)aminocarbonyl]-7-methoxybenzofuran (Compound 43)

Substantially the same procedure as in Example 1 was repeated using Compound IIai (0.80 g) obtained in Reference Example 35 to give Compound 43 (0.47 g, 39%) as a white solid.

Melting point: 216-218 °C
NMR($CDCl_3$, δ, ppm): 1.10(t, J=7Hz, 3H), 3.91(s, 2H), 4.00(q, J=7Hz, 2H), 4.08(s, 3H), 6.85(d, J=8Hz, 1H), 7.66(s, 1H), 7.71(d, J=8Hz, 1H), 7.75(s, 1H), 8.56(s, 2H)

Elemental analysis: $C_{19}H_{16}Cl_2N_2O_5$			
Found (%)	C:54.01,	H:3.75,	N:6.45
Calcd.(%)	C:53.92,	H:3.81,	N:6.62

Example 44

3-Carboxymethyl-4-[(3,5-dichloro-4-pyridyl)aminocarbonyl]-7-methoxybenzofuran (Compound 44)

Substantially the same procedure as in Example 9 was repeated using Compound 43 (0.64 g) obtained in Reference Example 43 to give Compound 44 (0.27 g, 47%) as a white solid.

Melting point: 270-278 °C
NMR(DMSO-d_6, δ, ppm): 3.79(s, 2H), 4.02(s, 3H), 7.09 (d, J=9Hz, 1H), 7.77(d, J=9Hz, 2H), 7.97(s, 1H), 8.74(s, 2H), 10.6-10.7(brs, 1H), 12.0-12.1(brs, 1H)

Elemental analysis: $C_{17}H_{12}Cl_2N_2O_5$			
Found (%)	C:51.38,	H:2.95,	N:6.92
Calcd.(%)	C:51.67,	H:3.06,	N:7.09

Example 45

4-[2-(3,5-Dichloro-4-pyridyl)ethyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 45)

(Step A) (±)-4-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 45a)

Under an argon atmosphere, a solution (20 ml) of 3,5-dichloro-4-methylpyridine (1.4 g) in THF was cooled to -78°C, and then a 1.69M solution of butyl lithium in hexane (6.3 ml) was dropwise added thereto, followed by stirring at the

same temperature for one hour. A solution (10 ml) of Compound IIa (2.0 g) obtained in Reference Example 1 in THF was slowly and dropwise added to the mixture, followed by stirring at -78°C for 2 hours and then at 0°C for one hour. The reaction solution was poured into water and the mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to give Compound 45a (3.3 g, 93.4%) as colorless crystals.

Melting point: 100-104 °C
NMR(DMSO-d_6, δ, ppm): 1.30(s, 3H), 1.38(s, 3H), 2.77 (d, J=15.8Hz, 1H), 3.04(d, J=15.8Hz, 1H), 3.04-3.11(m, 1H), 3.24-3.32(m, 1H), 3.71(s, 3H), 4.82-4.89 (m, 1H), 5.41(d, J=3.96Hz, 1H), 6.76(s, 2H), 8.55(s, 2H)
MASS(m/e): 369, 367(M^+), 207
IR(KBr, cm^{-1}): 3396(br), 1625, 1507

(Step B) (Compound 45)

Under an argon atmosphere, a solution (80 ml) of Compound 45a (3.0 g) obtained in Step A in methylene chloride was cooled to -78°C, and then boron trifluoride ether complex (2.0 ml) and triethylsilane (3.9 ml) were succcessively added thereto, followed by stirring at room temperature for 3 hours. The reaction solution was poured into a saturated aqueous solution of sodium bicarbonate and the mixture was extracted with chloroform. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give Compound 45 (1.57 g, 54.7%) as colorless crystals.

Melting point: 128-133 °C
NMR(DMSO-d_6, δ, ppm): 1.38(s, 6H), 2.68(t, J=7.25Hz, 2H), 2.91(s, 2H), 3.07(t, J=7.26Hz, 2H), 3.71(s, 3H), 6.54(d, J=8.25Hz, 1H), 6.72(d, J=8.25Hz, 1H), 8.58(s, 2H).
MASS(m/e): 353, 351(M^+), 191
IR(cm^{-1}): 1623, 1593, 1499

Elemental analysis: $C_{18}H_{19}Cl_2NO_2$			
Found (%)	C:61.37,	H:5.41,	N:3.92
Calcd.(%)	C:61.37,	H:5.44,	N:3.98

Example 46

7-Methoxy-2,2-dimethyl-4-[2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran (Compound 46)

(Step A) 4-[1-Hydroxy-2-(4-pyridyl)ethyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 46a)

Under an argon atmosphere, a solution (35 ml) of 4-methylpyridine (0.78 ml) in THF was cooled to -78°C, and then a 1.69M solution (5.17 ml) of butyl lithium in hexane was dropwise added thereto, followed by stirring at the same temperature for one hour. A solution (35 ml) of Compound IIa (1.5 g) obtained in Reference Example 1 in THF was slowly and dropwise added to the mixture, followed by stirring at -78°C for 2 hours and then at 0°C for one hour. The reaction solution was poured into water and the mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give Compound 46a (1.17 g, 53.8%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 1.29(s, 3H), 1.35(s, 3H), 2.75 (d, J=15.8Hz, 1H), 2.81-2.94(m, 2H), 2.94(d, J=15.8Hz, 1H), 3.71(s, 3H), 4.68(m, 1H), 5.27(d, J=4.0Hz, 1H), 6.76(s, 2H), 7.12(d, J=5.9Hz, 2H), 8.39(d, J=5.9Hz, 2H)
MASS(m/z): 299(M^+), 207

(Step B) (Compound 46)

Under an argon atmosphere, a solution (7 ml) of Compound 46a (0.2 g) obtained in Step A in methylene chloride was cooled to -78°C, and then boron trifluoride ether complex (0.17 ml) and triethylsilane (0.33 ml) were successively added thereto, followed by stirring at 0°C for 2 hours. The reaction solution was poured into a saturated aqueous solution of sodium bicarbonate and the mixture was extracted with chloroform. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give Compound 46 (0.11 g, 58.1%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 1.35(s, 6H), 2.70-2.82(m, 4H), 2.83(s, 2H), 3.70(s, 3H), 6.58(d, J=8.3Hz, 1H), 6.71(d, J=8.3Hz, 1H), 7.19(d, J=5.9Hz, 2H), 8.43 (d, J=5.9Hz, 2H)
IR(cm^{-1}): 1602, 1511, 1505, 1440
MASS(m/z): 283(M^+), 191

Elemental analysis: $C_{18}H_{21}NO_2 \cdot 0.3H_2O$			
Found (%)	C:74.87,	H:7.54,	N:4.85
Calcd.(%)	C:75.03,	H:7.44,	N:4.89

Example 47

(±) 7-Methoxy-2,2-dimethyl-7-methoxy-4-[1-phenyl-2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran (Compound 47)

(Step A) (±)-4-[1-Hydroxy-1-phenyl-2-(4-pyridyl)ethyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 47a)

Under an argon atmosphere, a solution of 4-methylpyridine (0.83 ml) in THF (50 ml) was cooled to -78°C, and then a 1.69M solution (5.0 ml) of butyl lithium in hexane was dropwise added thereto, followed by stirring at the same temperature for one hour. A solution of Compound IIaj (2.0 g) obtained in Reference Example 36 in THF (20 ml) was slowly and dropwise added to the mixture, followed by stirring at 0°C for 2 hours. The reaction solution was poured into water and the mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 50/1) to give Compound 47a (0.87 g, 32.5%) as yellowish brown crystals.

Melting point: 78-81°C
NMR(DMSO-d_6; δ, ppm): 1.14(s, 3H), 1.19(s, 3H), 2.39 (d, J=16.1Hz, 1H), 2.67(d, J=16.1Hz, 1H), 3.51(s, 2H), 3.72(s, 3H), 5.70(s, 1H), 6.74(d, J=8.6Hz, 1H), 6.81(d, J=5.9Hz, 2H), 6.92(d, J=8.6Hz, 1H), 7.15-7.19(m, 5H), 8.23(d, J=5.6Hz, 2H)
IR(KBr, cm^{-1}): 3500-3000(br), 1606, 1506, 1446, 1427
MASS(m/z): 375(M^+), 283

(Step B) (Compound 47)

Under an argon atmosphere, a solution of Compound 47a (0.4 g) obtained in Step A in methylene chloride (3 ml) was cooled to -78°C, and then boron trifluoride ether complex (0.3 ml) and triethylsilane (0.52 ml) were successively added thereto, followed by stirring at 0°C for 2 hours. The reaction solution was poured into a saturated aqueous solution of sodium bicarbonate and the mixture was extracted with chloroform. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 30/1) to give Compound 47 (0.27 g, 56.7%) as a yellowish brown oily substance.

NMR(DMSO-d_6; δ, ppm): 1.23(s, 3H), 1.30(s, 3H), 2.75 (s, 2H), 3.30-3.34(m, 2H), 3.68(s, 3H), 4.22(t, J=8.3Hz, 1H), 6.74(d, J=8.6Hz, 1H), 6.81(d, J=8.6Hz, 1H), 7.13(d, J=5.9Hz, 2H), 7.15-7.26(m, 5H), 8.34(d, J=5.9Hz, 2H)
IR(cm^{-1}): 1622, 1598, 1503, 1435

MASS(m/z): 359(M^+), 267

Example 48

7-Methoxy-2,2-dimethyl-4-(4-pyridylthiomethyl)-2,3-dihydrobenzofuran (Compound 48)

(Step A) 4-Hydroxymethyl-2,2-dimethyl-7-methoxy-2,3-dihydrobenzofuran (Compound 48a)

Compound IIa (4.0 g) obtained in Reference Example 1 was added to a suspension of lithium aluminium hydride (0.52 g) in ether (20 ml), followed by stirring at room temperature for one hour. The reaction solution was poured into ice and the reaction mixture was adjusted to pH 3 by adding dropwise 1N hydrochloric acid (10 ml). The ether layer was separated, washed with a saturated saline, and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 60/1) to give Compound 48a (0.32 g, 79.2%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 1.40(s, 6H), 2.97(s, 2H), 3.71 (s, 3H), 4.33(d, J=5.6Hz, 2H), 4.91(t, J=5.6Hz, 1H), 6.70(d, J=8.3Hz, 1H), 6.75(d, J=8.2Hz, 1H)
MASS(m/z): 208(M^+)

(Step B) (Compound 48)

Compound 48a (2.0 g) obtained in Step A was dissolved in methylene chloride (100 ml), and then diisopropylethylamine (5.0 ml) and methanesulfonyl chloride (0.8 ml) were added thereto, followed by stirring at room temperature for one hour. At the same temperature, 4-mercaptopyridine (1.4 g) was added to the reaction solution, and the mixture was stirred for 30 minutes. Water was added to the reaction solution and the mixture was extracted with methylene chloride. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 30/1) to give Compound 48 (1.4 g, 48.3%) as colorless crystals.

Melting point: 109-113 °C
NMR(DMSO-d_6; δ, ppm): 1.41(s, 6H), 3.06(s, 2H), 3.72 (s, 3H), 4.22(s, 2H), 6.74(d, J=8.4Hz, 1H), 6.80 (d, J=8.4Hz, 1H), 7.29(d, J=6.4Hz, 2H), 7.36(d, J=6.4Hz, 2H)
IR(KBr, cm^{-1}): 1572, 1506, 1450, 1439
MASS(m/z): 301(M^+), 191

Elemental analysis: $C_{17}H_{19}NO_2S \cdot 0.1H_2O$			
Found (%)	C:67.34,	H:6.38,	N:4.62
Calcd.(%)	C:67.30,	H:6.45,	N:4.93

Example 49

(±)-7-Methoxy-2,2-dimethyl-4-[1-phenyl-1-(4-pyridylthio)methyl]-2,3-dihydrobenzofuran (Compound 49)

Substantially the same procedure as in Step B of Example 48 was repeated using Compound IIaj-a (0.22 g) obtained in Step A of Reference Example 36 to give Compound 49 (0.20 g, 68.2%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.35(s, 3H), 1.40(s, 3H), 2.90 (d, J=15.3Hz, 1H), 3.13(d, J=15.8Hz, 1H), 3.32(s, 3H), 5.99(s, 1H), 6.77(d, J=8.4Hz, 1H), 6.83(d, J=8.4Hz, 1H), 7.18(d, J=7.0Hz, 2H), 7.26-7.48(m, 5H), 8.30(d, J=6.9Hz, 2H)
IR(cm^{-1}): 1600, 1574, 1506, 1439

Example 50

4-[2-(3,5-Dichloro-4-pyridyl)ethyl]-2,2-diethyl-7-methoxy-2,3-dihydrobenzofuran • methanesulfonate (Compound 50)

(Step A) (±)-4-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-2,2-diethyl-7-methoxy-2,3-dihydrobenzofuran (Compound 50a)

Substantially the same procedure as in Step A of Example 45 was repeated using Compound IIb (9.0 g) obtained in Reference Example 2 to give Compound 50a (7.8 g, 51.1%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 0.77(t, J=6.9Hz, 3H), 0.85(t, J=7.4Hz, 3H), 1.54-1.58 (m, 2H), 1.64(q, J=7.4Hz, 2H), 2.73(d, J=15.8Hz, 1H), 3.00(d, J=16.3Hz, 1H), 3.06-3.13(m, 1H), 3.25-3.30(m, 1H), 3.72(s, 3H), 4.86-4.91(m, 1H), 5.40 (d, J=4.0Hz, 1H), 6.73(s, 2H), 8.54(s, 2H)
MASS(m/e): 397, 395(M^+), 235

(Step B) (Compound 50)

Substantially the same procedure as in Step B of Example 45 was repeated using Compound 50a (4.6 g) obtained in Step A to give 4-[2-(3,5-dichloro-4-pyridyl)ethyl]-2,2-diethyl-7-methoxy-2,3-dihydrobenzofuran (2.6 g, 59.6%) as a colorless oily substance. The obtained colorless oily substance was dissolved in diethyl ether and methanesulfonic acid was added thereto. The precipitated crystals were collected by filtration, washed with diethyl ether, and dried to give Compound 50.

Melting point: 87-90°C
NMR(DMSO-d_6, δ, ppm): 0.83(t, d=7.4Hz, 6H), 1.64(q, d=7.4Hz, 4H), 2.49(s, 3H), 2.70(t, J=8.4Hz, 2H), 2.87(s, 2H), 3.08(t, J=8.4Hz, 2H), 3.71(s, 3H), 6.50(d, J=8.4Hz, 1H), 6.70(d, J=8.4Hz, 1H), 8.58 (s, 2H)
MASS(m/e): 381, 379(M^+), 219
IR(cm^{-1}): 2600-2200(br), 1506

Elemental analysis: $C_{20}H_{23}Cl_2NO_2 \cdot CH_3SO_3H$			
Found (%)	C:46.39,	H:5.54,	N:2.41
Calcd.(%)	C:46.15,	H:5.46,	N:2.45

MASS(m/z): 377(M^+), 267

Example 51 2,2-Diethyl-7-methoxy-4-[2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran • hydrochloride (Compound 51)

(Step A) (±)-2,2-Diethyl-4-[1-hydroxy-2-(4-pyridyl)ethyl]-7-methoxy-2,3-dihydrobenzofuran (Compound 51a)

Substantially the same procedure as in Step A of Example 46 was repeated using Compound IIb (20 g) obtained in Reference Example 2 to give Compound 51a (27.6 g, 98.7%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 0.74-0.86(m, 6H), 1.51-1.66(m, 4H), 2.71(d, J=15.8Hz, 1H), 2.79-2.96(m, 3H), 3.72(s, 3H), 4.71(m, 1H), 5.27(d, J=4.45Hz, 1H), 6.74(s, 2H), 7.12(d, J=5.9Hz, 2H), 8.39(d, J=5.9Hz, 2H)
MASS(m/e): 327(M^+), 235

(Step B) (Compound 51)

Substantially the same procedure as in Step B of Example 46 was repeated using Compound 51a (23 g) obtained in Step A to give 2,2-diethyl-7-methoxy-4-[2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran (8.46 g, 38.6%) as a colorless oily substance. The obtained colorless oily substance was dissolved in ethyl acetate and a hydrochloric acid-ethyl acetate solution was added thereto. The precipitated crystals were collected by filtration, washed with ethyl acetate, and dried to give Compound 51.

Melting point: 189-192 °C

NMR(DMSO-d_6, δ, ppm): 0.83(t, J=7.4Hz, 6H), 1.63(q, J=7.4Hz, 4H), 2.84(t, J=6.9Hz, 2H), 2.87(s, 2H), 3.13(t, J=6.9Hz, 2H), 3.71(s, 3H), 6.54(d, J=8.4Hz, 1H), 6.69(d, J=8.4Hz, 1H), 7.89(d, J=6.4Hz, 2H), 8.80(d, J=6.4Hz, 2H)
MASS(m/e): 312(M^+), 220
IR(cm^{-1}): 2970, 1635, 1593, 1508

Elemental analysis: $C_{20}H_{25}NO_2$ • HCl			
Found (%)	C:69.06,	H:7.69,	N:4.00
Calcd.(%)	C:69.05,	H:7.53,	N:4.03

Example 52

4-[2-(3,5-Dichloro-4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] • methanesulfonate (Compound 52)

(Step A) (±)-4-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 52a)

Substantially the same procedure as in Step A of Example 45 was repeated using Compound IIc (8.0 g) obtained in Reference Example 3 to give Compound 52a (7.0 g, 51.4%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 1.57-1.91(m, 8H), 2.93(d, J=16.2Hz, 1H), 3.06-3.13(m, 1H), 3.20(d, J=16.2Hz, 1H), 3.24-3.30(m, 1H), 3.32(s, 3H), 4.84-4.90(m, 1H), 5.40(d, J=3.6Hz, 1H), 6.74(s, 2H), 8.54(s, 2H)
MASS(m/e): 395, 393(M^+)

(Step B) (Compound 52)

Substantially the same procedure as in Step B of Example 45 was repeated using Compound 52a (2.8 g) obtained in Step A to give 4-[2-(3,5-dichloro-4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (1.1 g, 40%) as a pale-yellow oily substance. The obtained colorless oily substance was dissolved in diethyl ether and methanesulfonic acid was added thereto. The precipitated crystals were collected by filtration, washed with diethyl ether, and dried to give Compound 52.

Melting point: 130-133 °C
NMR(DMSO-d_6, δ, ppm): 1.67-1.91(m, 8H), 2.42(s, 3H), 2.69(t, J=7.3Hz, 2H), 3.4-3.09(m, 4H), 3.71(s, 3H), 6.54(d, J=8.3Hz, 1H), 6.71(d, J=8.3Hz, 1H), 8.58(s, 2H)
MASS(m/e): 379, 377(M^+), 217
IR(cm^{-1}): 2950(br), 1621, 1595, 1506

Elemental analysis: $C_{20}H_{21}Cl_2NO_2$ • CH_3SO_3H			
Found (%)	C:53.09,	H:5.42,	N:2.92
Calcd.(%)	C:53.17,	H:5.31,	N:2.95

Example 53

7-Methoxy-4-[2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] • hydrochloride (Compound 53)

(Step A) (±)-4-[1-Hydroxy-2-(4-pyridyl)ethyl-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 53a)

Substantially the same procedure as in Step A of Example 46 was repeated using Compound IIc (3.3 g) obtained in Reference Example 3 to give Compound 53a (1.3 g, 29%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 1.59-1.88(m, 8H), 2.78-2.96(m, 3H), 3.10(d, J=15.8Hz, 1H), 3.71(s, 3H), 4.70(q, J=4.3Hz, 1H), 5.26(d, J=4.3Hz, 1H), 6.75(s, 2H), 7.13(d, J=5.6Hz, 2H), 8.40(d, J=5.6Hz, 2H)
MASS(m/z): 325(M^+), 233

(Step B) (Compound 53)

Substantially the same procedure as in Step B of Example 46 was repeated using Compound 53a (0.5 g) obtained in Step A to give 7-methoxy-4-[2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (0.037 g, 7.8%) as a colorless oily substance. The obtained colorless oily substance was dissolved in ethyl acetate and a hydrochloric acid-ethyl acetate solution was added thereto. The precipitated crystals were collected by filtration, washed with ethyl acetate, and dried to give Compound 53.

Melting point: 167-169 °C
NMR(DMSO-d_6, δ, ppm): 1.68-1.79(m, 6H), 1.84-1.92(m, 2H), 2.83(t, J=7.9Hz, 2H), 3.08(s, 2H), 3.11(t, J=7.9Hz, 2H), 3.70(s, 3H), 6.56(d, J=8.4Hz, 1H), 6.70(d, J= 8.4Hz, 1H), 7.86(d, J=6.4Hz, 2H), 8.78(d, J=6.9Hz, 2H)
MASS(m/e): 309(M^+), 217
IR(cm^{-1}): 1635, 1507

Elemental analysis: $C_{20}H_{23}NO_2 \cdot HCl \cdot 0.3H_2O$			
Found (%)	C:68.48,	H:6.97,	N:3.91
Calcd.(%)	C:68.39,	H:7.06,	N:3.99

Example 54

4-[2-(3,5-Dichloro-4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] • methanesulfonate (Compound 54)

(Step A) (±)-4-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] (Compound 54a)

Substantially the same procedure as in Step A of Example 45 was repeated using Compound IId (6.0 g) obtained in Reference Example 4 to give Compound 54a (9.3 g, 85%) as a colorless oily substance.

Melting point: 104-108 C
NMR(DMSO-d_6, δ, ppm): 1.41(brs, 5H), 1.48-1.60(m, 5H), 2.66(d, J=15.7Hz, 1H), 2.98(d, J=15.8Hz, 1H), 3.06-3.13(m, 1H), 3.25-3.30(m, 1H), 3.73(s, 3H), 4.84-4.90(m, 1H), 5.41(d, J=3.9Hz, 1H), 6.74(s, 2H), 8.54(s, 2H)
MASS(m/e): 409, 407(M^+), 247

(Step B) (Compound 54)

Substantially the same procedure as in Step B of Example 45 was repeated using Compound 54a (5.5 g) obtained in Step A to give 4-[2-(3,5-dichloro-4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] (2.7 g, 51%) as a pale-yellow oily substance. The obtained colorless oily substance was dissolved in diethyl ether and meth-

anesulfonic acid was added thereto. The precipitated crystals were collected by filtration, washed with diethyl ether, and dried to give Compound 54.

Melting point: 91-94°C
NMR(DMSO-d_6, δ, ppm): 1.42(brs, 4H), 1.53-1.65(m, 6H), 1.42(s, 3H), 2.70(t, J=8.4Hz, 1H), 2.84(s, 2H), 3.08(t, J=8.4Hz, 1H), 3.72(s, 3H), 6.53(d, J=8.4Hz, 1H), 6.71(d, J=8.4Hz, 1H), 8.58(s, 2H)
MASS(m/e): 393, 391(M^+), 231
IR(cm^{-1}): 2930(br), 1506

Elemental analysis: $C_{21}H_{23}Cl_2NO_2 \cdot 1.5CH_3SO_3H$			
Found (%)	C:50.65,	H:5.53,	N:2.55
Calcd.(%)	C:50.37,	H:5.45,	N:2.61

Example 55

7-Methoxy-4-[2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] • hydrochloride (Compound 55)

(Step A) (±)-4-[2-Hydroxy-2-(4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] (Compound 55a)

Substantially the same procedure as in Step A of Example 46 was repeated using Compound IId (50 g) obtained in Reference Example 4 to give Compound 55a (64.3 g, 93.3%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 1.40-1.76(m, 10H), 2.65(d, J=15.8Hz, 1H), 2.77-2.96(m, 3H), 3.72(s, 3H), 4.66-4.73(m, 1H), 5.25(d, J=4.0Hz, 1H), 6.75(s, 2H), 7.11(dd, J=1.5, 4.5Hz, 2H), 8.38(dd, J=1.5, 4.5Hz, 2H)
MASS(m/e): 339(M^+)

(Step B) (Compound 55)

Substantially the same procedure as in Step B of Example 46 was repeated using Compound 55a (30 g) obtained in Step A to give 7-methoxy-4-[2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] (5.6 g, 20%) as a colorless oily substance. The obtained colorless oily substance was dissolved in ethyl acetate and a hydrochloric acid-ethyl acetate solution was added thereto. The precipitated crystals were collected by filtration, washed with ethyl acetate, and dried to give Compound 55.

Melting point: 176-179 °C
NMR(DMSO-d_6, δ, ppm): 1.43-1.53(m, 4H), 1.58-1.64(m, 6H), 2.81-2.85(m, 4H), 3.13(t, J=7.9Hz, 2H), 3.71(s, 3H), 6.55(d, J=8.4Hz, 1H), 6.70(d, J=8.4Hz, 1H), 7.89(d, J=6.4Hz, 2H), 8.81(d, J=6.9Hz, 2H)
MASS(m/e): 323(M^+), 231
IR(cm^{-1}): 1634, 1506, 1437

Elemental analysis: $C_{21}H_{25}NO_2 \cdot HCl$			
Found (%)	C:69.97,	H:7.42,	N:3.81
Calcd.(%)	C:70.08,	H:7.28,	N:3.89

Example 56

(±)-4-[2-(3,5-Dichloro-4-pyridyl)ethyl]-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound 56)

(Step A) 4-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound 56a) (a mixture of diastereomers)

Under an argon atmosphere, a solution (25 ml) of 3,5-dichloro-4-methylpyridine (1.1 g) in THF was cooled to -78°C, and then a 1.69M solution (4.9 ml) of butyl lithium in hexane was dropwise added to the solution, followed by stirring at the same temperature for one hour. A solution (25 ml) of Compound IIe (1.5 g) obtained in Reference Example 5 in THF was slowly and dropwise added to the mixture, followed by stirring at -78°C for one hour and then at 0°C for one hour. The reaction solution was poured into water and the mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 50/1) to give Compound 56a (2.35 g, 85.0%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): (main product) 1.22(d, J=6.93Hz, 3H), 3.10(d, J=4.95Hz, 1H), 3.24-3.32(m, 1H), 3.75(s, 3H), 4.13-4.14(m, 1H), 4.34(t, J=8.25Hz, 1H), 4.99-5.06(m, 1H), 5.39(d, J=5.28Hz, 1H), 6.86(d, J=8.35Hz, 1H), 7.00(d, J=8.58Hz, 1H), 8.57(s, 2H). (by-product) 1.22(d, J=6.93Hz, 3H), 3.05(d, J=4.95Hz, 1H), 3.24-3.32(m, 1H), 3.75(s, 3H), 4.16-4.17(m, 1H), 4.44(t, J=8.25Hz, 1H), 4.94-4.99(m, 1H), 5.28(d, J=4.29Hz, 1H), 6.82-6.88(m, 2H), 8.31(s, 2H)
IR(cm^{-1}): 1625, 1507, 1439
MASS(m/z): 355(M^++2), 353, 191

(Step B) (Compound 56)

Under an argon atmosphere, a solution (28 ml) of Compound 56a (1.0 g) obtained in Step A in methylene chloride was cooled to -78°C, and then boron trifluoride ether complex (0.69 ml) and triethylsilane (1.35 ml) were successively added thereto, followed by stirring at 0°C for 2 hours. The reaction solution was poured into a saturated aqueous solution of sodium bicarbonate and the mixture was extracted with chloroform. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 50/1) to give Compound 56 (0.62 g, 64.9%) as pale-yellow oily crystals.

NMR(DMSO-d_6, δ, ppm): 1.23(d, J=6.93Hz, 3H), 2.69-2.78(m, 2H), 3.08-3.15 (m, 2H), 3.46-3.52(s, 1H), 3.74(s, 3H), 4.15-4.20(m, 1H), 4.48(t, J=8.58Hz, 1H), 6.63(d, J=8.25Hz, 1H), 6.78(d, J=8.58Hz, 1H), 8.61(s, 2H)
IR(KBr, cm^{-1}): 1623, 1510, 1451, 1434
MASS(m/z): 339(M^++2), 337(M^+), 177

Elemental analysis: $C_{17}H_{17}Cl_2NO_2$			
Found (%)	C:60.37,	H:5.07,	N:4.14
Calcd.(%)	C:60.48,	H:5.26,	N:4.03

Example 57

(±)-7-Methoxy-3-methyl-4-[2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran (Compound 57)

(Step A) 4-[1-Hydroxy-2-(4-pyridyl)ethyl]-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound 57a) (a mixture of diastereomers)

Under an argon atmosphere, a solution (25 ml) of 4-methylpyridine (0.66 ml) in THF was cooled to -78°C, and then a 1.69M solution (4.9 ml) of butyl lithium in hexane was dropwise added thereto, followed by stirring at the same temperature for one hour. A solution (25 ml) of Compound IIe (1.5 g) obtained in Reference Example 5 in THF was slowly and dropwise added to the mixture, followed by stirring at -78°C for one hour and then at 0°C for one hour. The reaction

solution was poured into water and the mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 50/1) to give Compound 57a (1.64 g, 73.6%) as colorless crystals.

Melting point: 96-100 °C
NMR(DMSO-d_6, δ, ppm): (main product) 1.18(d, J=6.93Hz, 3H), 2.83-2.97(m, 2H), 3.74(s, 3H), 4.10-4.18(m, 1H), 4.31(t, J=8.54Hz, 1H), 4.73-4.84(m, 1H), 5.25(d, J=4.62Hz, 1H), 6.81-6.94(m, 2H), 7.16(d, J=4.62Hz, 2H), 8.41(d, J=4.62Hz, 2H). (by-product) 1.10(d, J=6.93Hz, 3H), 2.83-2.97(m, 2H), 3.74(s, 3H), 4.10-4.18(m, 1H), 4.44(t, J=8.25Hz, 1H), 4.73-4.84(m, 1H), 5.31(d, J=4.62Hz, 1H), 6.81-6.94(m, 2H), 7.23(d, J=4.61Hz, 2H), 7.43(d, J=4.61Hz, 2H)
IR(KBr, cm^{-1}): 1609, 1508, 1432
MASS(m/z): 285(M^+), 193

(Step B) (Compound 57)

Under an argon atmosphere, a solution (17 ml) of Compound 57a (0.6 g) obtained in Step A in methylene chloride was cooled to -78°C, and then boron trifluoride ether complex (0.42 ml) and triethylsilane (0.8 ml) were successively added thereto, followed by stirring at 0°C for 2 hours. The reaction solution was poured into a saturated aqueous solution of sodium bicarbonate and the mixture was extracted with chloroform. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 30/1) to give Compound 57 (0.042 g, 9.1%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.16(d, J=6.93Hz, 3H), 2.76-2.92(m, 4H), 3.40-3.47(m, 1H), 3.72(s, 3H), 4.11-4.16(m, 1H), 4.44(t, J=8.58Hz, 1H), 6.66(d, J=8.25Hz, 1H), 6.76(d, J=8.24Hz, 1H), 7.26(d, J=4.95Hz, 2H), 8.46(brs, 2H)
IR(cm^{-1}): 1602, 1510, 1435
MASS(m/z): 269(M^+), 177

Example 58

7-Methoxy-3-methyl-4-[1-phenyl-2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran (Compound 58) (a mixture of diastereomers)

(Step A) 4-[1-Hydroxy-1-phenyl-2-(4-pyridyl)ethyl]-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound 58a) (a mixture of diastereomers)

Under an argon atmosphere, a solution of 4-methylpyridine (0.83 ml) in THF (50 ml) was cooled to -78°C, and then a 1.69M solution (5.0 ml) of butyl lithium in hexane was added thereto, followed by stirring at the same temperature for one hour. A solution of Compound IIak (2.0 g) obtained in Reference Example 37 in THF (20 ml) was slowly and dropwise added to the mixture, followed by stirring at 0°C for 2 hours. The reaction solution was poured into water and the mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure to give a crude product of Compound 58a (0.87 g) as yellowish brown crystals. This crude product was subjected to a subsequent step without being purified.

(Step B) (Compound 58)

Under an argon atmosphere, a solution of Compound 58a (0.4 g) obtained in Step A in methylene chloride (3 ml) was cooled to -78°C, and then boron trifluoride ether complex (0.3 ml) and triethylsilane (0.52 ml) were successively added thereto, followed by stirring at 0°C for 2 hours. The reaction solution was poured into a saturated aqueous solution of sodium bicarbonate and the mixture was extracted with chloroform. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 30/1) to give Compound 58 (a mixture of diastereomers) (0.27 g, 56.7%) as pale-yellow crystals.

NMR(DMSO-d_6, δ, ppm): (main product) 0.61(d, J=6.93Hz, 3H), 3.23-3.33(m, 1H), 3.42(d, J=2.53Hz, 1H), 3.53(d, J=2.54Hz, 1H), 3.74(s, 3H), 3.97-3.99(m, 2H), 5.78(m, 1H), 6.77-6.86(m, 4H), 7.15-7.32(m, 5H), 8.24-8.26(m, 2H). (by-product) 0.77(d, J=6.93Hz, 3H), 3.27-3.55(m, 3H), 3.74(s, 3H), 3.97-3.99(m, 2H), 5.74(m, 1H), 6.77-6.86(m, 4H), 7.15-7.32(m, 5H), 8.21-8.26(m, 2H)

IR(cm^{-1}): 1605, 1506, 1447
MASS(m/z): 345(M^+)

Example 59

(±)-7-Methoxy-3-methyl-4-(4-pyridylthiomethyl)-2,3-dihydrobenzofuran (Compound 59)

(Step A) (±)-4-Hydroxymethyl-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound 59a)

Substantially the same procedure as in Step A of Example 48 was repeated using Compound IIe (7.0 g) obtained in Reference Example 5 to give Compound 59a (6.0 g, 85.0%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 1.19(d, J=6.93Hz, 3H), 3.53-3.59(m, 1H), 3.71(s, 3H), 4.14(dd, J=8.75Hz, 4.29Hz, 1H), 4.37-4.52(m, 3H), 4.99(t, J=5.61Hz, 1H), 6.77(s, 2H)
MASS(m/z): 194(M^+)

(Step B) (Compound 59)

Substantially the same procedure as in Step B of Example 48 was repeated using Compound 59a (1.5 g) obtained in Step A to give Compound 59 (1.5 g, 68%) as a colorless oily substance.

Melting point: 110-112 °C
NMR(DMSO-d_6, δ, ppm): 1.25(d, J=6.93Hz, 3H), 3.62-3.69(m, 1H), 3.74(s, 3H), 4.18(dd, J=3.96Hz, 8.74Hz, 1H), 4.30(s, 2H), 4.53(t, J=8.58Hz, 1H), 6.79(d, J=8.25Hz, 1H), 6.85(d, J=8.25Hz, 1H), 7.32(d, J=5.94Hz, 2H), 8.38(d, J=5.94Hz, 2H)
IR(KBr, cm^{-1}): 1618, 1575, 1506, 1439
MASS(m/z): 287(M^+), 177

Elemental analysis: $C_{16}H_{17}NO_2S$			
Found (%)	C:66.87,	H:5.96,	N:4.87
Calcd.(%)	C:66.94,	H:5.92,	N:5.08

Example 60

(±)-7-Methoxy-3-methyl-4-[1-phenyl-1-(4-pyridylthio)methyl]-2,3-dihydrobenzofuran (Compound 60A and Compound 60B)

Substantially the same procedure as in Step B of Example 48 was repeated using Compound IIak-a (2.6 g) obtained in Step A of Reference Example 37 to give Compound 60A and Compound 60B [60A (0.11 g, 3.1%) and 60B (0.19 g, 5.4%)] each as colorless crystals.

Compound 60A

Melting point: 59-62 °C
NMR(DMSO-d_6, δ, ppm): 1.31(d, J=6.93Hz, 3H), 3.57-3.63(m, 1H), 3.72(s, 3H), 4.20(dd, J=3.63Hz, 8.75Hz, 1H), 4.47(t, J=8.58Hz, 1H), 5.99(s, 1H), 6.82(d, J=8.58Hz, 1H), 6.90(d, J=8.24Hz, 1H), 7.17(d, J=5.94Hz, 2H), 7.23-7.36 (m, 3H), 7.51-7.54(m, 2H), 8.31(d, J=6.27Hz, 2H)
IR(KBr, cm^{-1}): 1620, 1572, 1504, 1433
MASS(m/z): 363(M^+), 253

Elemental analysis: $C_{22}H_{21}NO_2S \cdot 0.5H_2O$			
Found (%)	C:70.94,	H:5.95,	N:3.76
Calcd.(%)	C:70.85,	H:5.84,	N:3.85

Compound 60B

Melting point: 84-85 °C
NMR(DMSO-d_6, δ, ppm): 1.02(d, J=6.93Hz, 3H), 3.65-3.85(m, 1H), 3.73(s, 3H), 4.19(dd, J=2.97Hz, 8.91Hz, 1H), 4.52(t, J=8.58Hz, 1H), 6.09(s, 1H), 6.84(d, J=8.58Hz, 1H), 6.94(d, J=8.25Hz, 1H), 7.16(d, J=6.27Hz, 2H), 7.25-7.39(m, 3H), 7.49-7.52(m, 2H), 8.29(d, J=5.94Hz, 2H)
IR(KBr, cm^{-1}): 1619, 1569, 1506, 1437
MASS(m/z): 363(M^+), 253

Elemental analysis: $C_{22}H_{21}NO_2S \cdot 0.2H_2O$			
Found (%)	C:71.99,	H:5.88,	N:3.82
Calcd.(%)	C:71.95,	H:5.79,	N:3.90

Example 61

(±)-7-Methoxy-3-methyl-4-(4-pyridylaminomethyl)-2,3-dihydrobenzofuran (Compound 61)

Substantially the same procedure as in Step B of Example 48 was repeated using Compound 59a obtained in Step A of Example 59 and using 4-aminopyridine instead of 4-mercaptopyridine to give Compound 61 (26.5%) as colorless crystals.

Melting point: 138-145 °C
NMR(DMSO-d_6, δ, ppm): 1.23(d, J=6.43Hz, 3H), 3.59-3.79(m, 1H), 3.73(s, 3H), 4.14-4.31(m, 3H), 4.53 (t, J=8.90Hz, 1H), 6.52(d, J=4.95Hz, 2H), 6.73(d, J=8.41Hz, 1H), 6.79(d, J=8.41Hz, 1H), 6.98(brs, 1H), 8.01(d, J=5.44Hz, 2H)
IR(KBr, cm^{-1}): 1600, 1523, 1508, 1437
MASS(m/z): 270(M^+), 177

Example 62

(±)-4-[2-(3,5-Dichloro-4-pyridyl)-1-methoxyethyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 62)

p-Toluenesulfonic acid (1.0 g) was added to a solution (50 ml) of Compound 45a (2.0 g) obtained in Step A of Example 45 in methanol at room temperature, followed by heating under reflux. The reaction solution was cooled and then the solvent was distilled off under reduced pressure. A saturated aqueous solution of sodium bicarbonate was added to the residue, followed by extraction with chloroform. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to give Compound 62 (1.0 g, 48.2%) as a pale-yellow oily substance.

Melting point: 89-93 °C
NMR(DMSO-d_6, δ, ppm): 1.31(s, 3H), 1.41(s, 3H), 2.74 (d, J=15.51Hz, 1H), 3.04 (s, 3H), 3.07-3.15(m, 2H), 3.29-3.42(m, 1H), 3.73(s, 3H), 4.47(dd, J=6.59Hz, 7.59Hz, 1H), 6.64(d, J=8.58Hz, 1H), 6.79(d, J=8.25Hz, 1H), 8.56(s, 2H)

MASS(m/e): 383, 381(M^+), 221
IR(KBr, cm^{-1}): 1622, 1506, 1436

Elemental analysis: $C_{19}H_{21}Cl_2NO_3$			
Found (%)	C:59.96,	H:5.61,	N:3.56
Calcd.(%)	C:59.70,	H:5.54,	N:3.66

Example 63

(±)-4-[1-Cyano-2-(3,5-dichloro-4-pyridyl)ethyl]-2,2-dimethyl-7-methoxy-2,3-dihydrobenzofuran (Compound 63)

A solution (70 ml) obtained in Step A of Example 45 of Compound 45a (2.5 g) in methylene chloride was cooled to 0°C and then trimethylsilylcyanide (5.4 ml) and boron trifluoride ether complex (2.5 ml) were successively added thereto, followed by stirring at 0°C for 2 hours. The reaction solution was poured into a saturated aqueous solution of sodium bicarbonate and the mixture was extracted with chloroform. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 30/1) to give Compound 63 (0.61 g, 23.8%) as pale-yellow crystals.

Melting point: 158-162 °C
NMR(DMSO-d_6, δ, ppm): 1.34(s, 3H), 1.40(s, 3H), 2.83 (d, J=15.51Hz, 1H), 3.16(d, J=15.51Hz, 1H), 3.44-3.53(m, 2H), 3.74(s, 3H), 4.42(t, J=8.25, 1H), 6.80(d, J=8.25Hz, 1H), 6.87(d, J=7.92Hz, 1H), 8.66(s, 2H)
MASS(m/e): 378, 376(M^+), 216
IR(KBr, cm^{-1}): 2248, 1622, 1506, 1437

Elemental analysis: $C_{19}H_{18}Cl_2N_2O_2$			
Found (%)	C:60.42,	H:4.93,	N:7.54
Calcd.(%)	C:60.49,	H:4.81,	N:7.43

Example 64

(±)-4-[1-Cyano-2-(4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] • hydrochloride (Compound 64)

Substantially the same procedure as in Example 63 was repeated using Compound 53a (6.6 g) obtained in Step A of Example 53 to give (±)-4-[1-cyano-2-(4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (2.2 g, 32%) as a pale-yellow oily substance. Then, substantially the same procedure as in Example 51 was repeated using the obtained oily substance to give Compound 64.

Melting point: 187-189 °C
NMR(DMSO-d_6, δ, ppm): 1.73(s, 8H), 3.16(d, J=16.2Hz, 1H), 3.31(d, J=15.8Hz, 1H), 3.37-3.56(m, 2H), 3.74(s, 3H), 4.64(t, J=7.6Hz, 1H), 6.75(d, J=8.2Hz, 1H), 6.84(d, J=8.3Hz, 1H), 7.91(d, J=5.6Hz, 2H), 8.87(d, J=5.6Hz, 2H)
MASS(m/e): 334(M^+), 242
IR(KBr, cm^{-1}): 2243, 1633, 1508

Elemental analysis: $C_{21}H_{22}N_2O_2 \cdot HCl \cdot H_2O$			
Found (%)	C:67.38,	H:6.29,	N:7.19
Calcd.(%)	C:67.35,	H:6.30,	N:7.48

Example 65

(±)-4-[1-Cyano-1-methyl-2-(4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] • hydrochloride (Compound 65)

(Step A) (±)-4-[1-Hydroxy-1-methyl-2-(4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 65a)

Substantially the same procedure as in Example 46 was repeated using Compound IIan (2.7 g) obtained in Reference Example 40 to give Compound 65a (2.8 g, 74.7%) as a colorless oily substance.

(Step B) (Compound 65)

Substantially the same procedure as in Example 63 was repeated using Compound 65a (1.8 g) obtained in Step A to give (±)-4-[1-cyano-1-methyl-2-(4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (0.35 g, 18.9%) as a pale-yellow oily substance. Then, substantially the same procedure as in Example 51 was repeated using the obtained oily substance to give Compound 65.

Melting point: 142-144 °C
NMR(DMSO-d_6, δ, ppm): 1.74-1.94(m, 11H), 3.17(d, J=15.8Hz, 1H), 3.21(s, 2H), 3.40(d, J=16.3Hz, 1H), 3.75(s, 3H), 6.70(d, J=8.9Hz, 1H), 6.82(d, J=8.9Hz, 1H), 7.04(d, J=5.8Hz, 2H), 8.46(d, J=5.9Hz, 2H)
MASS(m/e): 348(M^+)

Example 66

(±)-7-Methoxy-4-[1-phenyl-2-(4-pyridyl)ethyl]-2-(4-pyridyl)benzofuran • hydrochloride (Compound 66)

Substantially the same procedure as in Example 47 was repeated using Compound IIal (0.45 g) obtained in Reference Example 38 to give (±)-7-methoxy-4-[1-phenyl-2-(4-pyridyl)ethyl]-2-(4-pyridyl)benzofuran (0.28 g, 50%) as a pale-yellow solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 66.

Melting point: 183-185 °C
NMR(DMSO-d_6, δ, ppm): 3.88(d-like, J=8Hz, 2H), 3.96(s, 3H), 4.93(t-like, J=8Hz, 1H), 7.08(d, J=8.5Hz, 1H), 7.1-7.4(m, 3H), 7.43(d, J=8.5Hz, 1H), 7.50 (d, J=7Hz, 2H), 7.94(d, J=6Hz, 2H), 8.33(d, J=6Hz, 2H), 8.55(s, 1H), 8.75(d, J=6Hz, 2H), 8.92(d, J=6Hz, 2H)
IR(KBr, cm^{-1}): 2840, 1630, 1590, 1560, 1200
MASS(m/e): 406(M^+), 348, 315

Elemental analysis: $C_{27}H_{22}NO_2 \cdot 2.0HCl \cdot 1.7H_2O$			
Found (%)	C:63.63,	H:5.33,	N:5.23
Calcd.(%)	C:63.58,	H:5.41,	N:5.49

Example 67

(E)-4-[2-(3,5-Dichloro-4-pyridyl)ethenyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 67)

p-Toluenesulfonic acid (0.8 g) was added to a suspension of Compound 45a (1.0 g) obtained in Step A of Example 45 in toluene (27 ml), followed by heating under reflux for 30 minutes. After being allowed to stand for cooling, a saturated aqueous solution of sodium bicarbonate was added to the reaction solution for neutralization, followed by extraction with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The resultant residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give Compound 67 (0.59 g, 62.2%) as yellow crystals.

Melting point: 114-118 °C
NMR(DMSO-d_6, δ, ppm): 1.44(s, 6H), 3.18(s, 2H), 3.80 (s, 3H), 6.91(d, J=8.57Hz, 1H), 6.92(d, J=16.82Hz, 1H), 7.16(d, J=8.25Hz, 1H), 7.36(d, J=16.82Hz, 1H), 8.64(s, 2H)
MASS(m/e): 351, 349(M^+)
IR(cm^{-1}): 1613, 1556, 1508

Elemental analysis: $C_{18}H_{17}Cl_2NO_2$			
Found (%)	C:61.75,	H:4.87,	N:4.00
Calcd.(%)	C:61.73,	H:4.89,	N:4.00

Example 68

(E)-7-Methoxy-2,2-dimethyl-4-[2-(4-pyridyl)ethenyl]-2,3-dihydrobenzofuran (Compound 68)

Substantially the same procedure as in Example 67 was repeated using Compound 46a (0.2 g) obtained in Step A of Example 46 to give Compound 68 (0.17 g, 90.2%) as yellow crystals.

Melting point: 145-149 °C
NMR(DMSO-d_6, δ, ppm): 1.45(s, 6H), 3.24(s, 2H), 3.78 (s, 3H), 6.88(d, J=8.58Hz, 1H), 6.97(d, J=16.83Hz, 1H), 7.15(d, J=8.58Hz, 1H), 7.39(d, J=16.49Hz, 1H), 7.54(d, J=5.94Hz, 2H), 8.51(d, J=5.94Hz, 2H)
IR(KBr, cm^{-1}): 1610, 1589, 1506, 1439
MASS(m/z): 281(M^+), 266

Elemental analysis: $C_{18}H_{19}NO_2 \cdot 0.2H_2O$			
Found (%)	C:75.87,	H:6.86,	N:4.92
Calcd.(%)	C:76.10,	H:6.86,	N:5.10

Example 69

7-Methoxy-2,2-dimethyl-4-[1-methyl-2-(4-pyridyl)ethenyl]-2,3-dihydrobenzofuran (Compound 69)

(Step A) (±)-4-[1-Hydroxy-1-methyl-2-(4-pyridyl)ethyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 69a)

Substantially the same procedure as in Step A of Example 65 was repeated using Compound IIan (2.7 g) obtained in Reference Example 39 to give Compound 69a (2.8 g, 74.4%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.22(s, 3H), 1.33(s, 3H), 1.45 (s, 3H), 2.83(d, J=16.2, 1H), 2.91(s, 2H), 3.16 (d, J=16.2Hz, 1H), 3.70(s, 3H), 6.67(s, 2H), 6.94(d, J=5.9Hz, 2H), 8.31(d, J=4.3Hz, 2H)

MASS(m/e): 313(M^+), 221

(Step B) (Compound 69)

Substantially the same procedure as in Example 67 was repeated using Compound 69a (0.6 g) obtained in Step A to give Compound 69 (0.52 g, 91.5%) as pale-yellow crystals.

Melting point: 85-87 °C
NMR(DMSO-d_6, δ, ppm): 1.42(s, 6H), 2.22(s, 3H), 3.15 (s, 2H), 3.77(s, 3H), 6.50(s, 1H), 6.85(s, 2H), 7.37(d, J=5.9Hz, 2H), 8.56(d, J=5.9Hz, 2H)
MASS(m/e): 295(M^+)
IR(KBr, cm^{-1}): 1614, 1593, 1504

Elemental analysis: $C_{19}H_{21}NO_2 \cdot 0.1H_2O$			
Found (%)	C:76.77,	H:7.22,	N:4.82
Calcd.(%)	C:76.79,	H:7.19,	N:4.71

Example 70

7-Methoxy-2,2-dimethyl-4-[1-phenyl-2-(4-pyridyl)ethenyl]-2,3-dihydrobenzofuran (Compound 70) (a mixture of E/Z)

Substantially the same procedure as in Example 67 was repeated using Compound 47a (0.3 g) obtained in Step A of Example 47 to give Compound 70 (0.28 g, 98.0%) as pale-yellow crystals.

Melting point: 110-113 °C
NMR(DMSO-d_6, δ, ppm): (main product;76%); 1.29(s, 6H), 2.56(s, 2H), 3.76(s, 3H), 6.69(d, J=8.58Hz, 1H), 6.74(s, 1H), 6.84(d, J=8.58Hz, 1H), 6.92(d, J=5.93Hz, 2H), 7.10-7.13(m, 2H), 7.36-7.38(m, 3H), 8.32(d, J=5.94Hz, 2H). (by-product;22%); 1.21(s, 6H), 2.43(s, 2H), 3.80(s, 3H), 6.54(d, J=8.25Hz, 1H), 6.87(d, J=8.26Hz, 1H), 6.96(d, J=5.94Hz, 2H), 7.06(m, 1H), 7.10-7.13(m, 2H), 7.36-7.38(m, 3H), 8.37(d, J=5.94Hz, 2H)
IR(KBr, cm^{-1}): 1618, 1592, 1506, 1433
MASS(m/z): 357(M^+)

Elemental analysis: $C_{24}H_{23}NO_2$			
Found (%)	C:80.64,	H:6.49,	N:3.92
Calcd.(%)	C:80.56,	H:6.61,	N:4.00

Example 71

(E)-2,2-Diethyl-7-methoxy-4-[2-(3,5-dichloro-4-pyridyl)ethenyl]-2,3-dihydrobenzofuran • methanesulfonate (Compound 71)

Substantially the same procedure as in Example 67 was repeated using Compound 50a (3.0 g) obtained in Step A of Example 50 to give (E)-2,2-diethyl-7-methoxy-4-[2-(3,5-dichloro-4-pyridyl)ethenyl]-2,3-dihydrobenzofuran (2.5 g, 90.5%) as yellow crystals. Then, substantially the same procedure as in Example 50 was repeated using tThe obtained crystals to give Compound 71.

Melting point: 137-141 °C
NMR(DMSO-d_6, δ, ppm): 0.87(t, d=7.4Hz, 6H), 1.71(q, d=7.4Hz, 4H), 2.36(s, 3H), 3.80(s, 3H), 6.84(d, J=8.4Hz, 1H), 6.94(d, J=16.8Hz, 1H), 7.14(d, J=8.4Hz, 1H), 7.37(d, J=16.8Hz, 1H), 8.64(s, 2H)

MASS(m/e): 379, 377(M^+)
IR(cm^{-1}): 1599, 1508

Elemental analysis: $C_{20}H_{21}Cl_2NO_2 \cdot CH_3SO_3H$			
Found (%)	C:52.93,	H:5.30,	N:2.88
Calcd.(%)	C:53.17,	H:5.32,	N:2.95

Example 72

(E)-2,2-Diethyl-7-methoxy-4-[2-(4-pyridyl)ethenyl]-2,3-dihydrobenzofuran • hydrochloride (Compound 72)

Substantially the same procedure as in Example 67 was repeated using Compound 51a (3.0 g) obtained in Step A of Example 51 to give (E)-2,2-diethyl-7-methoxy-4-[2-(4-pyridyl)ethenyl]-2,3-dihydrobenzofuran (2.6 g, 91%) as pale-yellow crystals. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 72.

Melting point: 236-239 °C
NMR(DMSO-d_6, δ, ppm): 0.90(t, J=7.4Hz, 6H), 1.72(q, J=7.4Hz, 4H), 3.27(s, 2H), 3.82(s, 3H), 6.93(d, J=8.9Hz, 1H), 7.25(d, J=8.4Hz, 1H), 7.26(d, J=14.8Hz, 1H), 7.84(d, J=16.3Hz, 1H), 8.19(d, J=6.9Hz, 2H), 8.79(d, J=6.4Hz, 2H)
MASS(m/e): 309(M^+), 280
IR(cm^{-1}): 1603, 1571, 1507, 1437

Elemental analysis: $C_{20}H_{23}NO_2 \cdot HCl$			
Found (%)	C:69.17,	H:7.08,	N:4.00
Calcd.(%)	C:69.45,	H:6.99,	N:4.05

Example 73

(E)-4-[2-(3,5-Dichloro-4-pyridyl)ethenyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] • methanesulfonate (Compound 73)

Substantially the same procedure as in Example 67 was repeated using Compound 52a (4.0 g) obtained in Step A of Example 52 to give (E)-4-[2-(3,5-dichloro-4-pyridyl)ethenyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (1.8 g, 46.1%) as yellow crystals. Then, substantially the same procedure as in Example 50 was repeated using the obtained crystals to give Compound 73.

Melting point: 155-158 °C
NMR(DMSO-d_6;δ, ppm): 1.75-1.79(m, 8H), 1.99-2.10(m, 2H), 2.38(s, 3H), 3.36(s, 2H), 3.80(s, 3H), 6.90(d, J=8.9Hz, 1H), 6.94(d, J=16.8Hz, 1H), 7.16(d, J=8.4Hz, 1H), 7.37(d, J=16.8Hz, 1H), 8.64(s, 2H)
MASS(m/e): 377, 375(M^+) 215
IR(cm^{-1}): 2935(br), 1589, 1566, 1506

Elemental analysis: $C_{20}H_{19}Cl_2NO_2 \cdot CH_3SO_3H$			
Found (%)	C:53.25,	H:4.90,	N:2.89
Calcd.(%)	C:53.40,	H:4.91,	N:2.97

Example 74

(E)-7-Methoxy-4-[2-(4-pyridyl)ethenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] • hydrochloride (Compound 74)

Substantially the same procedure as in Example 67 was repeated using Compound 53a (0.3 g) obtained in Step A of Example 53 to give (E)-7-methoxy-4-[2-(4-pyridyl)ethenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (0.2 g, 72%) as pale-yellow crystals. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 74.

Melting point: 229-231 °C
NMR(DMSO-d_6, δ, ppm): 1.65-1.90(m, 6H), 1.90-2.15(m, 2H), 3.47(s, 2H), 3.82(s, 3H), 6.95(d, J=8.6Hz, 1H), 7.24(d, J=16.5Hz, 1H), 7.27(d, J=8.6Hz, 1H), 7.83(d, J=16.5Hz, 1H), 8.17(d, J=6.6Hz, 2H), 8.78(d, J=6.3Hz, 2H)
MASS(m/z): 307(M^+)
IR(cm^{-1}): 1604, 1507

Elemental analysis: $C_{20}H_{21}NO_2 \cdot HCl \cdot H_2O$			
Found (%)	C:66.49,	H:6.69,	N:3.77
Calcd.(%)	C:66.38,	H:6.68,	N:3.87

Example 75

7-Methoxy-4-[1-methyl-2-(4-pyridyl)ethenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 75)

Substantially the same procedure as in Example 67 was repeated using Compound 65a (2.0 g) obtained in Step A of Example 65 to give Compound 75 (1.1 g, 57.3%) as yellow crystals.

Melting point: 85-87 °C
NMR(DMSO-d_6, δ, ppm): 1.74-1.90(m, 6H), 1.97-2.05(m, 2H), 2.36(s, 2H), 3.38(s, 3H), 3.79(s, 3H), 6.79 (s, 1H), 6.89(d, J=8.6Hz, 1H), 6.96(d, J= 8.2Hz, 1H), 8.02(d, J=6.6Hz, 2H), 8.84(d, J=6.6Hz, 2H)
MASS(m/e): 321(M^+)
IR(KBr, cm^{-1}): 1631, 1605, 1601

Elemental analysis: $C_{21}H_{23}NO_2 \cdot HCl \cdot 0.3H_2O$			
Found (%)	C:69.45,	H:7.05,	N:3.91
Calcd.(%)	C:69.43,	H:6.83,	N:3.86

Example 76

(E)-4-[2-(3,5-Dichloro-4-pyridyl)ethenyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] • methanesulfonate (Compound 76)

Substantially the same procedure as in Example 67 was repeated using Compound 54a (3.5 g) obtained in Step A of Example 54 to give (E)-4-[2-(3,5-dichloro-4-pyridyl)ethenyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] (2.7 g, 81%) as pale-yellow crystals. Then, substantially the same procedure as in Example 50 was repeated using the obtained crystals to give Compound 76.

Melting point: 108-109 °C
NMR($DMSO-d_6$, δ, ppm): 1.44-1.66(m, 4H), 1.70-1.76(m, 6H), 2.39(s, 3H), 3.14(s, 2H), 3.81(s, 3H), 6.20 (d, J=8.3Hz, 1H), 6.93(d, J=16.8Hz, 1H), 7.15(d, J=8.9Hz, 1H), 7.36(d, J=16.8Hz, 1H), 8.64(s, 2H)
MASS(m/e): 391, 389(M^+)
IR(cm^{-1}): 2932, 1595, 1507

Elemental analysis: $C_{21}H_{21}Cl_2NO_2 \cdot CH_3SO_3H \cdot 1.2H_2O$			
Found (%)	C:51.99,	H:5.21,	N:2.67
Calcd.(%)	C:52.01,	H:5.44,	N:2.76

Example 77

(E)-7-Methoxy-4-[2-(4-pyridyl)ethenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] • hydrochloride (Compound 77)

Substantially the same procedure as in Example 67 was repeated using Compound 55a (4 g) obtained in Step A of Example 55 to give (E)-7-methoxy-4-[2-(4-pyridyl)ethenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] (3.1 g, 82%) as pale-yellow crystals. Then, Substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 77.

Melting point: 234-239 °C
NMR($DMSO-d_6$, δ, ppm): 1.47-1.68(m, 4H), 1.72-1.99(m, 6H), 3.26(s, 2H), 3.83(s, 3H), 6.94(d, J=8.4Hz, 1H), 7.26(d, J=15.3Hz, 1H), 7.27(d, J=8.9Hz, 1H), 7.83(d, J=16.3Hz, 1H), 8.19(d, J=6.9Hz, 2H), 8.78(d, J=6.4Hz, 2H)
MASS(m/e): 321(M^+)
IR(cm^{-1}): 1600, 1511

Elemental analysis: $C_{21}H_{23}NO_2 \cdot HCl \cdot 0.3H_2O$			
Found (%)	C:69.51,	H:6.90,	N:3.84
Calcd.(%)	C:69.43,	H:6.83,	N:3.86

Example 78

(E)-(±)-4-[2-(3,5-Dichloro-4-pyridyl)ethenyl]-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound 78)

Substantially the same procedure as in Example 67 was repeated using Compound 56a (1.6 g) obtained in Step A of Example 56 to give Compound 78 (1.4 g, 92%) as yellow crystals.

Melting point: 117-118 °C

NMR(DMSO-d_6, δ, ppm): 1.23(s, J=6.93Hz, 3H), 3.68-3.74(m, 1H), 3.82(s, 3H), 4.26(dd, J=8.62Hz, 2.97Hz, 1H), 4.55(d, J=8.58Hz, 1H), 6.94(d, J=8.58Hz, 1H), 7.03(d, J=16.50Hz, 1H), 7.27(d, J=8.58Hz, 1H), 7.40(d, J=16.82Hz, 1H), 8.65(s, 2H)
MASS(m/e): 337, 335(M^+), 300
IR(cm^{-1}): 1616, 1507

Elemental analysis: $C_{17}H_{15}Cl_2NO_2$			
Found (%)	C:60.62,	H:4.45,	N:4.14
Calcd.(%)	C:60.73,	H:4.50,	N:4.17

Example 79

(E)-(±)-7-Methoxy-3-methyl-4-[2-(4-pyridyl)ethenyl]-2,3-dihydrobenzofuran (Compound 79)

Substantially the same procedure as in Example 67 was repeated using Compound 57a (0.25 g) obtained in Step A of Example 57 to give Compound 79(0.18 g, 95.3%) as yellow crystals.

Melting point: 93-95 °C
NMR(DMSO-d_6, δ, ppm): 1.21(d, J=6.93Hz, 3H), 3.80(s, 3H), 3.80-3.86(m, 1H), 4.26(dd, J=2.97Hz, 8.58Hz, 1H), 4.55(t, J=8.58Hz, 1H), 6.91(d, J=8.57Hz, 1H), 7.09(d, J=16.49Hz, 1H), 7.25(d, J=8.58Hz, 1H), 7.46(d, J=16.50Hz, 1H), 7.57(d, J=5.94Hz, 2H), 8.53(d, J=5.92Hz, 2H)
IR(KBr, cm^{-1}): 1612, 1591, 1506, 1459
MASS(m/z): 267(M^+)

Elemental analysis: $C_{17}H_{17}NO_2$			
Found (%)	C:76.38,	H:6.41,	N:5.24
Calcd.(%)	C:76.50,	H:6.36,	N:5.24

Example 80

(±)-7-Methoxy-3-methyl-4-[1-phenyl-2-(4-pyridyl)ethenyl]-2,3-dihydrobenzofuran (Compound 80) (an E/Z mixture)

Substantially the same procedure as in Example 67 was repeated using Compound 58a (1.5 g) obtained in Example 58 to give Compound 80 (1.3 g, 86.8%) as pale-yellow crystals.

Melting point: 103-105.5 °C
NMR(DMSO-d_6, δ, ppm): 1.07(d, J=6.60Hz, 3H), 2.92-3.10(m, 1H), 3.78(s, 3H), 4.08(dd, J=4.29Hz, 8.75Hz, 1H), 4.41(t, J=8.75Hz, 1H), 6.68(d, J=8.25Hz, 1H), 6.79(s, 1H), 6.86(d, J=8.25Hz, 1H), 6.95(d, J=5.28Hz, 2H), 7.13(m, 2H), 7.35(m, 3H), 8.33(d, J=5.61Hz, 2H)
IR(KBr, cm^{-1}): 1591, 1498, 1431
MASS(m/z): 343(M^+), 251

Elemental analysis: $C_{23}H_{21}NO_2$			
Found (%)	C:79.66,	H:6.26,	N:4.07
Calcd.(%)	C:79.61,	H:6.22,	N:4.04

Example 81

(E)-7-Methoxy-2-phenyl-4-[2-(4-pyridyl)ethenyl]benzofuran • hydrochloride (Compound 81)

(Step A) (±)-4-[1-Hydroxy-2-(4-pyridyl)ethyl]-7-methoxy-2-phenylbenzofuran (Compound 81a)

Substantially the same procedure as in Step A of Example 46 was repeated using Compound IIh (2.6 g) obtained in Reference Example 8 to give Compound 81a (2.33 g, 65.4%) as a yellowish white solid.

NMR($CDCl_3$, δ, ppm): 2.70(bs, 1H), 3.11(dd, J=6Hz, 14Hz, 1H), 3.21(dd, J=8Hz, 14Hz, 1H), 4.03(s, 3H), 5.15(dd, J=6Hz, 8Hz, 1H), 6.69(d, J=8Hz, 1H), 6.96(d, J=8Hz, 1H), 7.07(d, J=6Hz, 2H), 7.18(s, 1H), 7.37(t, J=7Hz, 1H), 7.44(dd, J=7Hz, 7Hz, 2H), 7.90(d, J=7Hz, 2H), 8.41(d, J=6Hz, 2H)
MASS(m/e): 345(M^+), 327, 253

(Step B) (Compound 81)

Substantially the same procedure as in Example 67 was repeated using Compound 81a (2.0 g) obtained in Step A to give (E)-7-methoxy-2-phenyl-4-[2-(4-pyridyl)ethenyl]benzofuran (1.10 g, 58.0%) as a yellow solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 81.

Melting point: 146-148 °C
NMR(DMSO-d_6, δ, ppm): 4.06(s, 3H), 7.11(d, J=9Hz, 1H), 7.4-7.6(m, 4H), 7.69(d, J=9Hz, 1H), 8.00(d, J=7Hz, 2H), 8.16(s, 1H), 8.19(d, J=18Hz, 1H), 8.30(d, J=7Hz, 2H), 8.84(d, J=7Hz, 2H)
IR(KBr, cm^{-1}): 1600, 1510, 1290, 1100
MASS(m/e): 328, 327(M^+)

Elemental analysis: $C_{22}H_{17}NO_2 \cdot 1.0HCl \cdot 1.0H_2O$			
Found (%)	C:69.25,	H:5.20,	N:3.73
Calcd.(%)	C:69.20,	H:5.28,	N:3.67

Example 82

(E)-4-[2-(3,5-Dichloro-4-pyridyl)ethenyl]-7-methoxy-2-(4-pyridyl)benzofuran (Compound 82)

(Step A) (±)-4-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-7-methoxy-2-(4-pyridyl)benzofuran (Compound 82a)

Substantially the same procedure as in Step A of Example 45 was repeated using Compound IIf (4.00 g) obtained in Reference Example 6 to give Compound 82a (3.91 g, 59.6%) as a yellowish white solid.

NMR(DMSO-d_6, δ, ppm): 3.23(dd, J=5Hz, 13Hz, 1H), 3.45 (dd, J=8Hz, 13Hz, 1H), 3.97(s, 3H), 5.22(m, 1H), 5.74(d, J=4Hz, 1H), 6.95(d, J=8Hz, 1H), 7.11(d, J=8Hz, 1H), 7.69(s, 1H), 7.84(d, J=6Hz, 2H), 8.54(s, 2H), 8.69(d, 6Hz, 2H)
MASS(m/e): 416, 414(M^+)

(Step B) (Compound 82)

Substantially the same procedure as in Example 67 was repeated using Compound 82a (1.50 g) obtained in Step A to give Compound 82 (0.847 g, 59.1%) as a yellow solid.

Melting point: 204-206 °C
NMR($CDCl_3$, δ, ppm): 4.10(s, 3H), 6.91(d, J= 8Hz, 1H), 7.16(d, J=17Hz, 1H), 7.46(d, J=8Hz, 1H), 7.50(s, 1H), 7.77(d, J=17Hz, 1H), 7.77(d, J=6Hz, 2H), 8.52(s, 2H), 8.71(d, J=6Hz, 2H)

IR(KBr, cm^{-1}): 1615, 1550, 1290, 1180
MASS(m/e): 400, 398, 396(M^+)

Elemental analysis: $C_{21}H_{14}N_2O_2Cl_2$			
Found (%)	C:63.32,	H:3.51,	N:6.98
Calcd.(%)	C:63.51,	H:3.55,	N:7.05

Example 83

(E)-7-Methoxy-2-(4-pyridyl)-4-[2-(4-pyridyl)ethenyl]benzofuran • 2 hydrochloride (Compound 83)

(Step A) (±)-4-[1-Hydroxy-2-(4-pyridyl)ethyl]-7-methoxy-2-(4-pyridyl)benzofuran (Compound 83a)

Substantially the same procedure as in Step A of Example 46 was repeated using Compound IIf (1.0 g) obtained in Reference Example 6 to give Compound 83a (1.11 g, 81.4%) as a yellowish white solid.

NMR(DMSO-d_6, δ, ppm): 3.15(d, J=7Hz, 2H), 3.97(s, 3H), 5.17(t, J=7Hz, 1H), 5.64(bs, 1H), 6.97(d, J=8Hz, 1H), 7.16(d, J=8Hz, 1H), 7.52(d, J=6Hz, 2H), 7.91(d, J=6Hz, 2H), 8.00(s, 1H), 8.56(d, J=6Hz, 2H), 8.71(d, J=6Hz, 2H)
MASS(m/e): 346(M^+), 328, 254

(Step B) (Compound 83)

Substantially the same procedure as in Example 67 was repeated using Compound 83a (2.8 g) obtained in Step A to give (E)-7-methoxy-2-(4-pyridyl)-4-[2-(4-pyridyl)ethenyl]benzofuran (1.60 g, 60.4%) as a yellow solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 83.

Melting point: 200-203 °C
NMR(DMSO-d_6, δ, ppm): 4.08(s, 3H), 7.27(d, J=8Hz, 1H), 7.69(d, J=17Hz, 1H), 7.75(d, J=8Hz, 1H), 8.25(d, J=17Hz, 1H), 8.36(d, J=6Hz, 2H), 8.43(d, J=5Hz, 2H), 8.88(d, J=6Hz, 2H), 8.98(d, J=5Hz, 2H), 9.02(s, 1H)
IR(KBr, cm^{-1}): 1640, 1600, 1560, 1500
MASS(m/e): 329(M^+ +1), 313

Elemental analysis: $C_{21}H_{16}N_2O_2$ • 2.0HCl • $1.6H_2O$			
Found (%)	C:58.61,	H:5.05,	N:6.45
Calcd.(%)	C:58.64,	H:4.97,	N:6.51

Example 84

(E)-4-[2-(3,5-Dichloro-4-pyridyl)ethenyl]-7-methoxy-2-(2-pyridyl)benzofuran (Compound 84)

(Step A) (±)-4-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-7-methoxy-2-(2-pyridyl)benzofuran (Compound 84a)

Substantially the same procedure as in Step A of Example 45 was repeated using Compound IIg (3.40 g) obtained in Reference Example 7 to give Compound 84a (4.51 g, 80.9%) as a yellowish white solid.

NMR(DMSO-d_6, δ, ppm): 3.22(dd, J=5Hz, 14Hz, 1H), 3.45 (dd, J=9Hz, 14Hz, 1H), 3.98(s, 3H), 5.21(ddd, J=5Hz, 5Hz, 9Hz, 1H), 5.73(d, J=5Hz, 1H), 6.91(d, J=10Hz, 1H), 7.10(d, J=10Hz, 1H), 7.40(m, 1H), 7.62(s, 1H), 7.9-8.0(m, 2H), 8.55(s, 2H), 8.70 (dd, J=2Hz, 5Hz, 1H)

MASS(m/e): 416, 414(M^+), 254

(Step B) (Compound 84)

Substantially the same procedure as in Example 67 was repeated using Compound 84a (0.60 g) obtained in Step A to give Compound 84 (0.28 g, 49.5%) as a yellow solid.

Melting point: 157-158 °C
NMR($CDCl_3$, δ, ppm): 4.10(s, 3H), 6.90(d, J= 8Hz, 1H), 7.20(d, J=17Hz, 1H), 7.27(m, 1H), 7.47(d, J=8Hz, 1H), 7.75(s, 1H), 7.82(m, 1H), 7.82(d, J=17Hz, 1H), 8.02(d, J=8Hz, 1H), 8.51(s, 2H), 8.69(dd, J=1Hz, 4Hz, 1H).
IR(KBr, cm^{-1}): 1610, 1550, 1510, 1290
MASS(m/e): 400, 398, 396(M^+)

Elemental analysis: $C_{21}H_{14}N_2O_2Cl_2$			
Found (%)	C:63.81,	H:3.57,	N:6.91
Calcd.(%)	C:63.51,	H:3.55,	N:7.05

Example 85

(E)-7-Methoxy-2-(2-pyridyl)-4-[2-(4-pyridyl)ethenyl]benzofuran • 2 hydrochloride (Compound 85)

(Step A) (±)-4-[1-Hydroxy-2-(4-pyridyl)ethyl]-7-methoxy-2-(2-pyridyl)benzofuran (Compound 85a)

Substantially the same procedure as in Step A of Example 46 was repeated using Compound IIg (3.0 g) obtained in Reference Example 7 to give Compound 85a (2.10 g, 51.1%) as a yellowish white solid.

NMR($DMSO-d_6$, δ, ppm): 3.04(d, J=6Hz, 2H), 3.96(s, 3H), 5.15(dt, J=4Hz, 6Hz, 1H), 5.53(d, J=4Hz, 1H), 6.92(d, J=8Hz, 1H), 7.12(d, J=8Hz, 1H), 7.26(d, J=6Hz, 2H), 7.41(dd, J=5Hz, 9Hz, 1H), 7.74(s, 1H), 7.9-8.0(m, 2H), 8.41(d, J=6Hz, 2H), 8.68(d, J=5Hz, 1H)
MASS(m/e): 346(M^+), 253, 252

(Step B) (Compound 85)

Substantially the same procedure as in Example 67 was repeated using Compound 85a (2.1 g) obtained in Step A to give (E)-7-methoxy-2-(2-pyridyl)-4-[2-(4-pyridyl)ethenyl]benzofuran (0.58 g, 29.2%) as a yellow solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 85.

Melting point: 192-195 °C
NMR(D_2O, δ, ppm): 4.11(s 3H), 6.69(d, J=17Hz, 1H), 6.89(d, J=8Hz, 1H), 7.25(d, J=8Hz, 1H), 7.27(d, J=17Hz, 1H), 7.54(s, 1H), 7.72(dd, J=5Hz, 7Hz, 1H), 7.92(d, J=6Hz, 2H), 7.99(d, J=8Hz, 1H), 8.31(dd, J=7Hz, 8Hz, 1H), 8.55(d, J=5Hz, 1H), 8.72(d, J=6Hz, 2H)
IR(KBr, cm^{-1}): 1610, 1560, 1280
MASS(m/e): 328(M^+)

Elemental analysis: $C_{21}H_{16}N_2O_2$ • 2.0HCl • 1.4H_2O			
Found (%)	C:59.12,	H:4.73,	N:6.51
Calcd.(%)	C:59.14,	H:4.91,	N:6.57

Example 86

(E)-4-[2-Cyano-2-(4-pyridyl)ethenyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 86)

Compound IIa (2.3 g) obtained in Reference Example 1 was suspended in glacial acetic acid, and sodium acetate (2.3 g) and 4-pyridylacetonitrile (1.6 ml) were successively added thereto, followed by stirring at 110°C for one hour. The reaction solution was poured into water and the mixture was extracted with ethyl acetate. The collected organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (ethyl acetate/toluene = 1/9) and recrystallized from ethanol to give Compound 86 (1.6 g, 46%) as pale-yellow crystals.

Melting point: 150-163 °C
NMR(DMSO-d_6, δ, ppm): 1.44(s, 6H), 3.33(s, 2H), 3.84 (s, 3H), 7.04(d, J=8.57Hz, 1H), 7.71(d, J=5.94Hz, 1H), 7.73(d, J=8.25Hz, 1H), 7.98(s, 1H), 8.67(d, J=6.27Hz, 1H)
MASS(m/e): 306(M^+)
IR(KBr, cm^{-1}): 2206, 1578, 1508

Elemental analysis: $C_{19}H_{18}N_2O_2$			
Found (%)	C:74.63,	H:5.95,	N:9.25
Calcd.(%)	C:74.49,	H:5.92,	N:9.14

Example 87

(E)-4-[2-Ethoxycarbonyl-2-(4-pyridyl)ethenyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 87)

Substantially the same procedure as in Example 86 was repeated using Compound IIa (2.0 g) obtained in Reference Example 1 and using ethyl ester of 4-pyridineacetic acid instead of 4-pyridylacetonitrile to give Compound 87 (2.5 g, 73.2%) as dark brown crystals.

Melting point: 98-100 °C
NMR(DMSO-d_6, δ, ppm): 1.20(t, J=7.26Hz, 3H), 1.38(s, 6H), 3.02(s, 2H), 3.68(s, 3H), 4.19(q, J=7.26Hz, 2H), 6.15(d, J=8.57Hz, 1H), 6.60(d, J=8.57Hz, 1H), 7.23(d, J=5.93Hz, 2H), 7.71(s, 1H), 8.57(d, J=5.93Hz, 2H)
MASS(m/e): 353(M^+), 280
IR(KBr, cm^{-1}): 1706, 1596, 1508

Example 88

4-(2,2-Dicyanoethenyl)-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 88)

Compound IIa (2.0 g) obtained in Reference Example 1 was suspended in glacial acetic acid, and sodium acetate (1.9 g) and malonitrile (0.8 ml) were successively added thereto, followed by stirring at 110°C for one hour. The reaction solution was poured into water, and the precipitated crystals were collected by filtration, washed with water, and dried under reduced pressure. The obtained crude crystals were purified by silica gel column chromatography (chloroform) to give Compound 88 (2.4 g, 94.5%) as pale-yellow crystals.

Melting point: 198-200 °C
NMR(DMSO-d_6, δ, ppm): 1.43(s, 6H), 3.24(s, 2H), 3.87 (s, 3H), 7.12(d, J=8.6Hz, 1H), 7.75(d, J=8.6Hz, 1H), 8.19(s, 1H)
MASS(m/e): 254(M^+)
IR(KBr, cm^{-1}): 2218, 1619, 1589

Elemental analysis: $C_{15}H_{14}N_2O_2$			
Found (%)	C:70.95,	H:5.57,	N:10.96
Calcd.(%)	C:70.85,	H:5.55,	N:11.02

Example 89

4-(2-Cyano-2-ethoxycarbonylethenyl)-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 89)

Substantially the same procedure as in Example 88 was repeated using Compound IIa (2.0 g) obtained in Reference Example 1 and using ethyl cyanoacetate instead of malonitrile to give Compound 89 (2.8 g, 96.5%) as a dark brown oily substance.

Melting point: 112-117 °C
NMR(DMSO-d_6, δ, ppm): 1.30(t, J=6.9Hz, 3H), 1.44(s, 6H), 3.23(s, 2H), 3.86(s, 3H), 4.30(q, J=6.9Hz, 2H), 7.09(d, J=8.9Hz, 1H), 7.83(d, J=8.6Hz, 1H), 8.09(s, 1H)
MASS(m/e): 301(M^+)
IR(KBr, cm^{-1}): 2218, 1718, 1590

Elemental analysis: $C_{17}H_{19}NO_4$			
Found (%)	C:67.80,	H:6.41,	N:4.82
Calcd.(%)	C:67.76,	H:6.35,	N:4.65

Example 90

(E)-7-Methoxy-4-[2-(4-pyridylaminocarbonyl)ethenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 90)

(Step A) (E)-4-(2-Ethoxycarbonylethenyl)-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 90a)

Triethyl phosphonoacetate (10.5 g) was suspended in THF (70 ml), and potassium t-butoxide (3.74 g) was added thereto under ice-cooling, followed by stirring at room temperature for 30 minutes. After cooling the reaction solution with ice again, a solution of Compound IIc (3.1 g) obtained in Reference Example 3 in THF (20 ml) was slowly and dropwise added thereto under ice-cooling, followed by stirring at room temperature for one hour. Water was added to the reaction solution and the mixture was extracted with ether. The collected organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (chloroform) to give Compound 90a (3.51 g, 87.0%) as white crystals.

Melting point: 81-91 °C
NMR(DMSO-d_6, δ, ppm): 1.25(t, J=6.4Hz, 3H), 1.30-2.22 (m, 8H), 3.35(s, 2H), 3.79(s, 3H), 4.17(d, J=7.4Hz, 2H), 6.28(d, J=16.3Hz, 1H), 6.83(d, J=8.4Hz, 1H), 7.18(d, J=8.4Hz, 1H), 7.53(d, J=16.3Hz, 1H)
MASS(m/e): 302(M^+), 229

(Step B) (E)-4-(2-Carboxyethenyl)-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 90b)

A mixture of Compound 90a (3.5 g) obtained in Step A, a 4N aqueous solution (35.0 ml) of sodium hydroxide, and ethanol (150 ml) was stirred at room temperature for 15 hours. The solvent was distilled off and the residue was dissolved in water. Concentrated hydrochloric acid was dropwise added to the solution, and a precipitate was collected by filtration, washed with water, and dried to give Compound 90b (2.38 g, 74.9%) as white crystals.

Melting point: 212-215 °C
NMR(DMSO-d_6, δ, ppm): 1.75-1.96(m, 8H), 3.33(s, 2H), 3.79(s, 3H), 6.23(d, J=15.8Hz, 1H), 6.86(d, J=8.4Hz, 1H), 7.15(d, J=8.4Hz, 1H), 7.48(d, J=16.3Hz, 1H), 12.26(brs, 1H)
MASS(m/e): 274(M^+)

(Step C) (Compound 90)

Compound 90b (0.3 g) obtained in Step B was suspended in a mixed solvent of methylene chloride (6 ml) and dioxane (1 ml), and dicyclohexylcarbodiimide (DCC) (0.23 g) and 4-aminopyridine (0.11 g) were added thereto after cooling the suspension to 0°C, followed by stirring at room temperature for 6 hours. Water was added to the mixture followed by extraction with chloroform. The collected organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (chloroform) to give Compound 90 (0.22 g, 64.5%) as pale-yellow crystals.

Melting point: 124-128 °C
NMR(DMSO-d_6, δ, ppm): 1.77-1.90(m, 6H), 1.90-2.10(s, 2H), 3.39(s, 2H), 3.80(s, 3H), 6.60(d, J=15.8Hz, 1H), 6.91(d, J=8.4Hz, 1H), 7.09(d, J=8.4Hz, 1H), 7.55(d, J=15.8Hz, 1H), 7.57(d, J=5.7Hz, 2H), 8.45(d, J=5.9Hz, 1H), 10.47 (s, 1H)
IR(KBr, cm^{-1}): 1592, 1506
MASS(m/e): 350(M^+), 257

Elemental analysis: $C_{21}H_{22}N_2O_3 \cdot 0.4H_2O$			
Found (%)	C:70.52,	H:6.41,	N:7.60
Calcd.(%)	C:70.53,	H:6.43,	N:7.83

Example 91

(E)-7-Methoxy-4-[2-[4-(methoxycarbonyl)phenyl-1-ylaminocarbonyl]ethenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 91)

Compound 90b (0.9 g) obtained in Step B of Example 90 was suspended in a mixed solvent of methylene chloride (18 ml) and dioxane (4 ml), and dicyclohexylcarbodiimide (DCC) (0.69 g) and ethyl 4-aminobenzoate (0.55 g) were added thereto after cooling the suspension to 0°C, followed by stirring at room temperature for 6 hours. Water was added to the mixture followed by extraction with chloroform. The collected organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (chloroform) to give Compound 91 (0.36 g, 26.9%) as white crystals.

Melting point: 119-123 °C
NMR(DMSO-d_6, δ, ppm): 1.77-1.90(m, 6H), 1.90-2.10(m, 2H), 3.38(s, 2H), 3.80(s, 3H), 3.83(s, 3H), 6.67 (d, J=15.8Hz, 1H), 6.91(d, J=8.4Hz, 1H), 7.08(d, J=8.4Hz, 1H), 7.52(d, J=15.8Hz, 1H), 7.82(d, J=8.9Hz, 2H), 7.95(d, J=8.4Hz, 2H), 10.45(s, 1H)
IR(KBr, cm^{-1}): 1699, 1608, 1506
MASS(m/e): 407(M^+)

Elemental analysis: $C_{24}H_{25}NO_5 \cdot 0.1H_2O$			
Found (%)	C:70.43,	H:6.37,	N:3.44
Calcd.(%)	C:70.43,	H:6.20,	N:3.42

Example 92

(E)-4-[2-(4-Carboxyphenylaminocarbonyl)ethenyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 92)

A mixture of Compound 91 (0.25 g) obtained in Example 91, a 4N aqueous solution (1.6 ml) of sodium hydroxide, and dioxane (2.5 ml) was heated under reflux for 2 hours. The reaction solution was cooled, poured into water, and the mixture was adjusted to pH 3 by 6N hydrochloric acid. The precipitated crystals were collected by filtration, washed with water, and dried to give Compound 92 (0.43 g, 17.8%) as white crystals.

Melting point: 266-269 °C
NMR(DMSO-d_6, δ, ppm): 1.65-1.90(s, 6H), 1.90-2.10(m, 2H), 3.38(s, 2H), 3.80(s, 3H), 6.63(d, J=15.8Hz, 1H), 6.91(d, J=8.4Hz, 1H), 7.09(d, J=8.4Hz, 1H), 7.52(d, J=15.3Hz, 1H), 7.80(d, J=8.9Hz, 2H), 7.92(d, J=8.9Hz, 1H), 10.43(s, 1H).
IR(KBr, cm^{-1}): 1682, 1596
MASS(m/e): 394(M^+ +1), 257

Elemental analysis: $C_{23}H_{23}NO_5 \cdot 0.1H_2O$			
Found (%)	C:69.85,	H:5.92,	N:3.54
Calcd.(%)	C:69.85,	H:6.13,	N:3.52

Example 93

(E)-7-Methoxy-4-{2-[3-(methoxycarbony)phenylaminocarbonyl]ethenyl}-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 93)

Substantially the same procedure as in Example 91 was repeated using Compound 90b (0.9 g) obtained in Step B of Example 90 and methyl 3-aminobenzoate (0.55 g) to give Compound 93 (0.68 g, 50.8%) as white crystals.

Melting point: 88-91 °C
NMR(DMSO-d_6, δ, ppm): 1.77-1.90(s, 6H), 1.90-2.10(m, 2H), 3.39(s, 2H), 3.80(s, 3H), 3.87(s, 3H), 6.60 (d, J=15.8Hz, 1H), 6.91(d, J=8.6Hz, 1H), 7.08(d, J=8.3Hz, 1H), 7.46-7.55(m, 2H), 7.66(d, J=7.9Hz, 1H), 7.97(d, J=7.9Hz, 1H), 8.36(s, 1H), 10.37(s, 1H)
IR(KBr, cm^{-1}): 1724, 1608
MASS(m/e): 407(M^+), 257

Elemental analysis: $C_{24}H_{25}NO_5 \cdot 0.6H_2O$			
Found (%)	C:68.69,	H:6.10,	N:3.34
Calcd.(%)	C:68.92,	H:6.31,	N:3.35

Example 94

(E)-4-[2-(4-Carboxyphenylaminocarbonyl)ethenyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 94)

Substantially the same procedure as in Example 92 was repeated using Compound 93 (0.48 g) obtained in Example 93 to give Compound 94 (0.34 g, 73.5%) as white crystals.

Melting point: >290°C

NMR(DMSO-d_6, δ, ppm): 1.77-1.90(m, 6H), 1.90-2.10(m, 2H), 3.39(s, 2H), 3.80(s, 3H), 6.60(d, J=15.8Hz, 1H), 6.91(d, J=8.6Hz, 1H), 7.08(d, J=8.2Hz, 1H), 7.43-7.63(m, 1H), 7.64(d, J=6.6Hz, 1H), 7.95(d, J=7.9Hz, 1H), 8.30(s, 1H), 10.32(s, 1H), 10.32(s, 1H), 12.98

IR(KBr, cm^{-1}): 1683, 1610

MASS(m/e): 393(M^+), 257

Elemental analysis: $C_{23}H_{23}NO_5$			
Found (%)	C:70.23,	H:5.93,	N:3.60
Calcd.(%)	C:70.21,	H:5.89,	N:3.56

Example 95

4-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound 95)

Compound 45a (3.0 g) obtained in Step A of Example 45 was dissolved in methylene chloride (80 ml), and a powder of silica gel (15 g) and pyridinium chlorochromate (PCC) (2.1 g) were added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was filtered and the obtained filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 30/1) to give Compound 95 (1.3 g, 44.9%) as pale-yellow crystals.

Melting point: 127-131 °C

NMR(DMSO-d_6, δ, ppm): 1.40(s, 6H), 3.24(s, 2H), 3.87 (s, 3H), 4.71(s, 2H), 7.03(d, J=8.58Hz, 1H), 7.79(d, J=8.58Hz, 1H), 8.66(s, 2H)

MASS(m/e): 367, 365(M^+), 205

IR(cm^{-1}): 1675, 1613, 1575

Elemental analysis: $C_{18}H_{17}Cl_2NO_3$			
Found (%)	C:58.91,	H:4.60,	N:3.73
Calcd.(%)	C:59.03,	H:4.68,	N:3.82

Example 96

7-Methoxy-2,2-dimethyl-4-[1-oxo-2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran (Compound 96)

Substantially the same procedure as in Example 95 was repeated using Compound 46a (4.5 g) obtained in Step A of Example 46 to give Compound 96 (0.7 g, 15.5%) as pale-yellow crystals.

Melting point: 107-111 °C

NMR(DMSO-d_6, δ, ppm): 1.39(s, 6H), 3.26(s, 2H), 3.85 (s, 3H), 4.37(s, 2H), 6.98(d, J=8.58Hz, 1H), 7.27(d, J=5.61Hz, 2H), 7.66(d, J=8.57Hz, 1H), 8.49(d, J=5.61Hz, 2H)

MASS(m/e): 297(M^+), 205

IR(cm^{-1}): 1675, 1608, 1578, 1511

Elemental analysis: $C_{18}H_{19}NO_3 \cdot 0.1H_2O$			
Found (%)	C:72.37,	H:6.56,	N:4.61
Calcd.(%)	C:72.27,	H:6.47,	N:4.68

Example 97

4-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-2,2-diethyl-7-methoxy-2,3-dihydrobenzofuran (Compound 97)

Under an argon atmosphere, a solution (50 ml) of 3,5-dichloro-4-methylpyridine (7.8 g) in THF was cooled to -78°C, and then a 1.69M solution (29 ml) of butyl lithium in hexane was dropwise added thereto, followed by stirring at the same temperature for one hour. A solution (40 ml) of Compound IIk (4.0 g) obtained in Reference Example 11 in THF was slowly and dropwise added to the mixture, followed by stirring at 0°C for 2 hours and then at room temperature for 3 hours. The reaction solution was poured into water and the mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform) to give Compound 97 (5.0 g, 4.2%) as a white solid.

Melting point: 164-166 °C
NMR(DMSO-d_6, δ, ppm): 0.83(t, d=7.4Hz, 6H), 1.64(q, d=7.4Hz, 4H), 3.20(s, 2H), 3.88(s, 3H), 4.71(s, 2H), 7.01(d, J=8.4Hz, 1H), 7.76(d, J=8.9Hz, 1H), 8.65(s, 2H)
MASS(m/e): 395, 393(M^+), 233
IR(cm^{-1}): 2970(br), 1677, 1615, 1574

Elemental analysis: $C_{20}H_{21}Cl_2NO_3$			
Found (%)	C:60.84,	H:5.37,	N:3.53
Calcd.(%)	C:60.92,	H:5.37,	N:3.55

Example 98

2,2-Diethyl-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran • hydrochloride (Compound 98)

Under an argon atmosphere, a solution (50 ml) of 4-methylpyridine (4.8 ml) in THF was cooled to -78°C, and then a 1.69M solution (29 ml) of butyl lithium in hexane was dropwise added thereto, followed by stirring at the same temperature for one hour. A solution (40 ml) of Compound IIk (4.0 g) obtained in Reference Example 11 in THF was slowly and dropwise added to the mixture, followed by stirring at 0°C for 2 hours and then at room temperature for 2 hours. The reaction solution was poured into water and the mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 20/1) to give 2,2-diethyl-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran as a colorless oily substance. Then, substantially the same procedure as in Example 51 was repeated using the obtained oily substance to give Compound 98.

Melting point: 185-191 °C
NMR(DMSO-d_6, δ, ppm): 0.84(t, J=7.4Hz, 6H), 1.67(d, J=7.4Hz, 4H), 3.24(s, 2H), 3.88(s, 3H), 4.78(s, 2H), 7.02(d, J=8.4Hz, 1H), 7.67(d, J=8.4Hz, 1H), 7.95(d, J=6.4Hz, 2H), 8.86(d, J=6.4Hz, 2H)
MASS(m/e): 325(M^+), 233
IR(cm^{-1}): 1671, 1611, 1574, 1505

Elemental analysis: $C_{20}H_{23}NO_3 \cdot HCl$			
Found (%)	C:66.36,	H:6.85,	N:3.85
Calcd.(%)	C:66.38,	H:6.69,	N:3.87

Example 99

4-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 99)

Substantially the same procedure as in Example 97 was repeated using Compound III (1.0 g) obtained in Reference Example 12 to give Compound 99 (0.42 g, 42.0%) as pale-yellow crystals.

Melting point: 159-162 °C
NMR(DMSO-d_6, δ, ppm): 1.70-1.78(m, 6H), 1.90-2.09(m, 2H), 3.42(s, 2H), 3.88(s, 3H), 4.71(s, 3H), 7.03 (d, J=8.9Hz, 1H), 7.78(d, J=8.4Hz, 1H), 8.65(s, 2H)
MASS(m/e): 393, 391(M^+), 231
IR(cm^{-1}): 1675, 1612, 1576

Elemental analysis: $C_{20}H_{19}Cl_2NO_3 \cdot 0.3H_2O$			
Found (%)	C:60.40,	H:4.80,	N:3.50
Calcd.(%)	C:60.40,	H:4.97,	N:3.52

Example 100

7-Methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] • hydrochloride (Compound 100)

Substantially the same procedure as in Example 98 was repeated using Compound III (4.0 g) obtained in Reference Example 12 to give 7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (2.1 g, 42.6%) as a pale-yellow oily substance. Then, substantially the same procedure as in Example 51 was repeated using the obtained oily substance to give Compound 100.

Melting point: 215-219 °C
NMR(DMSO-d_6, δ, ppm): 1.70-1.79(m, 6H), 1.90-1.97(m, 2H), 3.44(s, 2H), 3.87 (s, 3H), 4.77(s, 2H), 7.03(d, J=6.4Hz, 2H), 7.68(d, J=6.4Hz, 2H), 7.94 (d, J= 8.4Hz, 1H), 8.86(d, J=8.9Hz, 1H)
MASS(m/e): 323(M^+), 294
IR(cm^{-1}): 1670, 1610, 1510

Elemental analysis: $C_{20}H_{21}NO_3 \cdot HCl \cdot 0.2H_2O$			
Found (%)	C:66.21,	H:6.26,	N:3.79
Calcd.(%)	C:66.09,	H:6.21,	N:3.85

Example 101

4-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] (Compound 101)

Substantially the same procedure as in Example 97 was repeated using Compound IIm (4.0 g) obtained in Reference Example 13 to give Compound 101 (4.3 g, 72.3%) as pale-yellow crystals.

Melting point: 149-151 °C
NMR(DMSO-d_6, δ, ppm): 1.43(brs, 4H), 1.62-1.72(m, 6H), 3.20(s, 2H), 3.89(s, 3H), 4.71(s, 2H), 7.02(d, J=8.4Hz, 1H), 7.78(d, J=8.9Hz, 1H), 8.65(s, 2H)
MASS(m/e): 407, 405(M^+), 245

IR(cm^{-1}): 2841(br), 1678, 1578

Elemental analysis: $C_{20}H_{19}Cl_2NO_3 \cdot 0.2H_2O$			
Found (%)	C:60.54,	H:4.77,	N:3.56
Calcd.(%)	C:60.68,	H:4.94,	N:3.54

Example 102

7-Methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] • hydrochloride (Compound 102)

Substantially the same procedure as in Example 98 was repeated using Compound IIm (3.0 g) obtained in Reference Example 13 to give 7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] (2.0 g, 54.9%) as a pale-yellow oily substance. Then, substantially the same procedure as in Example 51 was repeated using the obtained oily substance to give Compound 102.

Melting point: 193-196 °C
NMR(DMSO-d_6, δ, ppm): 1.43(brs, 4H), 1.50-1.72(m, 6H), 3.23(s, 2H), 3.88(s, 3H), 4.80(s, 2H), 7.03(d, J=8.9Hz, 1H), 7.68(d, J=8.4Hz, 1H), 7.97(d, J=6.4Hz, 2H), 8.88(d, J=6.4Hz, 2H).
MASS(m/e): 338(M^+), 245
IR(cm^{-1}): 1674, 1610, 1510

Elemental analysis: $C_{21}H_{23}NO_3 \cdot HCl \cdot 0.1H_2O$			
Found (%)	C:66.99,	H:6.58,	N:3.68
Calcd.(%)	C:67.14,	H:6.49,	N:3.73

Example 103

(±)-4-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound 103)

Substantially the same procedure as in Example 95 was repeated using Compound 56a (1.0 g) obtained in Step A in Example 56 to give Compound 103 (0.5 g, 51.3%) as pale-yellow crystals.

Melting point: 99-104 °C
NMR(DMSO-d_6, δ, ppm): 1.08(d, J=6.93Hz, 3H), 3.77-3.90(m, 1H), 3.90(s, 3H), 4.28(dd, J=2.64Hz, 8.58Hz, 1H), 4.49(t, J=8.58Hz, 1H), 4.68(d, J=17.49Hz, 1H), 4.80(d, J=17.81Hz, 1H), 7.05(d, J=8.57Hz, 1H), 7.84(d, J=8.58Hz, 1H), 8.67(s, 2H)
IR(KBr, cm^{-1}): 1684, 1612, 1579, 1506, 1433
MASS(m/z): 353(M^++2), 351(M^+), 191

Elemental analysis: $C_{17}H_{15}Cl_2NO_3$			
Found (%)	C:57.97,	H:4.29,	N:3.98
Calcd.(%)	C:57.93,	H:4.37,	N:3.77

Example 104

(±)-7-Methoxy-3-methyl-4-[1-oxo-2-(4-pyridyl)ethyl]-2,3-dihydrobenzofuran (Compound 104)

Substantially the same procedure as in Example 95 was repeated using Compound 57a (0.6 g) obtained in Step A in Example 57 to give Compound 104 (0.03 g, 4,2%) as pale-yellow crystals.

Melting point: 111-117 °C
NMR(DMSO-d_6, δ, ppm): 1.08(d, J=6.93Hz, 3H), 3.77-3.86(m, 1H), 3.86(s, 3H), 4.27(dd, J=2.64Hz, 8.75Hz, 1H), 4.40(s, 2H), 4.46(t, J=8.75Hz, 1H), 7.00(d, J=8.58Hz, 1H), 7.28(d, J=4.29Hz, 2H), 7.72(d, J=8.58Hz, 1H), 8.50(d, J=4.29Hz, 2H)
IR(KBr, cm^{-1}): 1686, 1613, 1579, 1508, 1433
MASS(m/z): 283(M^+), 191 Elemental analysis: $C_{17}H_{17}NO_3 \cdot 0.3H_2O$ Found (%)C:70.72,H:6.14,N:4.85 Calcd.(%)C:70.54,H:6.10,N:4.46

Example 105

(±)-cis-6-Methoxy-9-[1-oxo-2-(4-pyridyl)ethyl]-1,2,3,4,4a,9b-hexahydrodibenzofuran • hydrochloride (Compound 105)

Substantially the same procedure as in Example 98 was repeated using Compound IIn (0.4 g) obtained in Reference Example 14 to give (±)-cis-6-methoxy-9-[1-oxo-2-(4-pyridyl)ethyl]-1,2,3,4,4a,9b-hexahydrodibenzofuran (0.34 g, 68%) as a pale-yellow oily substance. Then, substantially the same procedure as in Example 51 was repeated using the obtained oily substance to give Compound 105.

Melting point: 225-233 °C
NMR($CDCl_3$, δ, ppm): 0.80-1.00(m, 1H), 1.10-1.36(m, 1H), 1.40-1.85(m, 1H), 1.98-2.12(m, 1H), 2.35-2.52(m, 1H), 3.45-3.64(m, 1H), 3.99(s, 3H), 4.58 (s, 2H), 4.50-4.65(m, 1H), 6.89(d, J=9Hz, 1H), 7.51(d, J=9Hz, 1H), 7.83(d, J=7Hz, 2H), 8.73(d, J=7Hz, 2H)

Elemental analysis: $C_{20}H_{21}NO_3 \cdot HCl$			
Found (%)	C:66.59,	H:6.15,	N:4.02
Calcd.(%)	C:66.76,	H:6.16,	N:3.89

Example 106

2-Cyano-4-[2-(3,5-dichloro-4-pyridyl)-1-oxoethyl]-7-methoxybenzofuran (Compound 106)

(Step A) 2-Cyano-4-[2-(3,5-dichloro-4-pyridyl)-1-hydroxyethyl]-7-methoxybenzofuran (Compound 106a)

Substantially the same procedure as in Step A of Example 45 was repeated using Compound IIi (2.0 g) obtained in Reference Example 9 to give Compound 106a (2.3 g, 63.2%) as pale-yellow crystals.

NMR(DMSO-d_6, δ, ppm): 3.15-3.22(m, 1H), 3.30-3.50(m, 1H), 3.94(s, 3H), 5.13-5.20(m, 1H), 5.83(d, J=4.0Hz, 1H), 7.10(d, J=8.3Hz, 1H), 7.16(d, J=7.9Hz, 1H), 8.12(s, 1H), 8.55(s, 2H)
MASS(m/e): 362(M^+)

(Step B) (Compound 106)

Substantially the same procedure as in Example 95 was repeated using Compound 106a (1.1 g) obtained in Step A to give Compound 106 (0.27 g, 25.0%) as white crystals.

Melting point: 197-199 °C
NMR(DMSO-d_6, δ, ppm): 4.12(s, 3H), 4.88(s, 2H), 7.39 (d, J=8.6Hz, 1H), 8.41(s, 1H), 8.47(d, J=8.3Hz, 1H), 8.69(s, 2H).

MASS(m/e): 362, 360(M^+), 200
IR(cm^{-1}): 1675, 1557

Elemental analysis: $C_{17}H_{10}Cl_2N_2O_3$			
Found (%)	C:56.62,	H:2.77,	N:7.54
Calcd.(%)	C:56.53,	H:2.79,	N:7.76

Example 107

2-Benzoyl-7-methoxy-4-(1-oxo-2-phenylethyl)benzofuran (Compound 107)

Compound IIag-a (1.0 g) obtained in Step A of Reference Example 33 and phenylacetyl chloride (0.79 ml) were dissolved in dry dichloromethane (50 ml), the solution was cooled to 0°C, and titanium tetrachloride (1.3 ml) was dropwise added thereto, followed by stirring at the same temperature. After 5 minutes, the reaction was stopped by adding distilled water, and the reaction solution was extracted with diethylether. Then, the organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1) to give Compound 107 (0.94 g, 64.0%) as a pale-yellow solid.

NMR($CDCl_3$, δ, ppm): 4.10(s, 3H), 4.37(s, 2H), 6.93(d, J=8.5Hz, 1H), 7.2-7.4 (m, 5H), 7.51(dd, J=7.5Hz, 8Hz, 2H), 7.61(t, J=8Hz, 1H), 7.91(d, J=8.5Hz, 1H), 8.01(d, J=7.5Hz, 2H), 8.26(s, 1H)
MASS(m/e): 370(M^+), 279, 251

Elemental analysis: $C_{24}H_{18}O_4$		
Found (%)	C:77.97,	H:4.94
Calcd.(%)	C:77.82,	H:4.91

Example 108

2-Benzoyl-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran (Compound 108)

Substantially the same procedure as in Example 107 was repeated using Compound IIag-a obtained in Step A of Reference Example 33 to give Compound 108 as a pale-yellow solid.

NMR($CDCl_3$, δ, ppm): 4.13(s, 3H), 4.35(s, 2H), 6.98(d, J=8Hz, 1H), 7.23(d, J= 5.5Hz, 2H), 7.52(dd, J=7Hz, 8Hz, 2H), 7.63(t, J=7Hz, 1H), 7.98(d, J=8Hz, 2H), 8.03(d, J=8Hz, 1H), 8.24(s, 1H), 8.57(d, J=5.5Hz, 2H)
MASS(m/e): 371(M^+), 279

Example 109

2-Butyl-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran • hydrochloride (Compound 109)

Substantially the same procedure as in Example 98 was repeated using Compound IIo (1.3 g) obtained in Reference Example 15 to give 2-butyl-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran (0.42 g, 42%) as pale-yellow crystals. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 109.

Melting point: 212-218 °C
NMR($CDCl_3$, δ, ppm): 0.941(t, J=7Hz, 3H), 1.30-1.55(m, 2H), 1.65-1.85(m, 2H), 2.83(t, J=7Hz, 2H), 4.12 (s, 3H),

4.65(s, 2H), 6.82(d, J=9Hz, 1H), 7.12(s, 1H), 7.84(d, J=9Hz, 1H), 7.87(d, J=6Hz, 2H), 8.72(d, J=6Hz, 2H)

Elemental analysis: $C_{20}H_{21}NO_3HCl0.2H_2O$			
Found (%)	C:66.03,	H:6.09,	N:3.77
Calcd.(%)	C:66.09,	H:6.21,	N:3.85

Example 110

7-Methoxy-2-(2-methylpropyl)-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran • hydrochloride (Compound 110)

Substantially the same procedure as in Example 98 was repeated using Compound IIp (1.8 g) obtained in Reference Example 16 to give 7-methoxy-2-(2-methylpropyl)-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran (1.2 g, 56%) as white crystals. Then, Substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 110.

Melting point: 193-198 °C
NMR($CDCl_3$, δ, ppm): 0.970(d, J=7Hz, 6H), 2.05-2.20(m, 1H), 2.70(d, J=7Hz, 2H), 4.12(s, 3H), 4.64(s, 2H), 6.82(d, J=9Hz, 1H), 7.13(s, 1H), 7.77-7.88 (m, 3H), 8.71(d, J=7Hz, 2H)

Elemental analysis: $C_{20}H_{21}NO_3HCl$			
Found (%)	C:66.64,	H:6.16,	N:3.90
Calcd.(%)	C:66.76,	H:6.16,	N:3.89

Example 111

7-Methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-2-phenylbenzofuran • hydrochloride (Compound 111)

Substantially the same procedure as in Example 98 was repeated using Compound IIs (2.30 g) obtained in Reference Example 19 to give 7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-2-phenylbenzofuran (1.30 g, 26.6%) as a white solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 111.

NMR(DMSO-d_6, δ, ppm): 4.12(s, 3H), 4.94(s, 2H), 7.16 (d, J=8.5Hz, 1H), 7.4-7.6(m, 3H), 7.90(s, 1H), 7.97(d, J=7Hz, 2H), 8.04(d, J=5.5Hz, 2H), 8.18(d, J=8.5Hz, 1H), 8.92(d, J=5.5Hz, 2H)
MASS(m/e): 343(M^+), 251, 223

Elemental analysis: $C_{22}H_{17}NO_3 \cdot HCl \cdot 0.1H_2O$			
Found (%)	C:69.07,	H:4.73,	N:3.80
Calcd.(%)	C:69.24,	H:4.81,	N:3.67

Example 112

2-(2-Ethylphenyl)-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran • hydrochloride (Compound 112)

Substantially the same procedure as in Example 98 was repeated using Compound IIt (3.0 g) obtained in Reference Example 20 to give 2-(2-ethylphenyl)-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran (1.00 g, 27.8%) as a white solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 112.

Melting point: 186-188 °C
NMR(DMSO-d_6, δ, ppm): 1.19(t, J=7Hz, 3H), 2.87(q, J=7Hz, 2H), 4.11(s, 3H), 4.93(s, 2H), 7.18(d, J=8.5Hz, 1H), 7.3-7.5(m, 3H), 7.61(s, 1H), 7.75 (d, J=7.5Hz, 1H), 8.02(d, J=6Hz, 2H), 8.21(d, J=8.5Hz, 1H), 8.89(d, J=6Hz, 2H)
IR(KBr, cm^{-1}): 2960, 2920, 1654, 1618, 1573
MASS(m/e): 371(M^+), 279

Elemental analysis: $C_{24}H_{21}NO_3$ • HCl			
Found (%)	C:70.69,	H:5.45,	N:3.46
Calcd.(%)	C:70.66,	H:5.45,	N:3.43

Example 113

2-(2-Isopropylphenyl)-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran • hydrochloride (Compound 113)

Substantially the same procedure as in Example 98 was repeated using Compound IIu (2.50 g) obtained in Reference Example 21 to give 2-(2-isopropylphenyl)-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran (1.10 g, 37.0%) as a white solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 113.

Melting point: 184-185 °C
NMR(DMSO-d_6, δ, ppm): 1.23(d, J=6.5Hz, 6H), 3.44(sep, J=6.5Hz, 1H), 4.11(s, 3H), 4.94(s, 2H), 7.17(d, J=8.5Hz, 1H), 7.37(dd, J=5Hz, 7Hz, 1H), 7.4-7.6 (m, 2H), 7.53(s, 1H), 7.62(d, J=7Hz, 1H), 8.02(d, J=6Hz, 2H), 8.22(d, J=8.5Hz, 1H), 8.90(d, J=6Hz, 2H)
IR(KBr, cm^{-1}): 2960, 2950, 1653, 1618, 1577
MASS(m/e): 385(M^+), 293

Elemental analysis: $C_{25}H_{23}NO_3$ • HCl			
Found (%)	C:71.00,	H:5.73,	N:3.35
Calcd.(%)	C:71.16,	H:5.74,	N:3.32

Example 114

4-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-7-methoxy-2-(4-pyridyl)benzofuran • 2 hydrochloride (Compound 114)

Substantially the same procedure as in Example 97 was repeated using Compound IIq (2.0 g) obtained in Reference Example 17 to give 4-[2-(3,5-dichloro-4-pyridyl)-1-oxoethyl]-7-methoxy-2-(4-pyridyl)benzofuran (0.18 g, 9.1%) as a white solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 114.

Melting point: 263-266 °C

NMR(DMSO-d_6, δ, ppm): 4.16(s, 3H), 4.91(s, 2H), 7.34 (d, J=9Hz, 1H), 8.40(d, J=9Hz, 1H), 8.50(d, J=6Hz, 2H), 8.66(s, 1H), 8.70(s, 2H), 8.97(d, J=6Hz, 2H).
IR(KBr, cm^{-1}): 1675, 1630, 1585, 1350
MASS(m/e): 416, 414, 412(M^+), 253, 252

Elemental analysis: $C_{21}H_{14}N_2O_3Cl_2 \cdot 2HCl \cdot 0.8H_2O$			
Found (%)	C:50.36,	H:3.68,	N:5.45
Calcd.(%)	C:50.38,	H:3.54,	N:5.59

Example 115

7-Methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-2-(4-pyridyl)benzofuran • 2 hydrochloride (Compound 115)

Substantially the same procedure as in Example 98 was repeated using Compound IIq (2.6 g) obtained in Reference Example 17 to give 7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-2-(4-pyridyl)benzofuran (1.78 g, 55.9%) as a white solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 115.

Melting point: 225-228 °C
NMR(DMSO-d_6, δ, ppm): 4.13(s, 3H), 5.00(s, 2H), 7.32 (d, J=9Hz, 1H), 8.07(d, J=6Hz, 2H), 8.25(d, J=9Hz, 1H), 8.44(d, J=7Hz, 2H), 8.57(s, 1H), 8.9-9.0(m, 4H)
IR(KBr, cm^{-1}): 1665, 1635, 1610, 1520, 1350
MASS(m/e): 344(M^+), 252

Elemental analysis: $C_{21}H_{16}N_2O_3 \cdot 2.0HCl \cdot 2.0H_2O$			
Found (%)	C:55.74,	H:4.82,	N:6.10
Calcd.(%)	C:55.64,	H:4.89,	N:6.18

Example 116

4-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-7-methoxy-2-(2-pyridyl)benzofuran • 2 hydrochloride (Compound 116)

Substantially the same procedure as in Example 97 was repeated using Compound IIr (3.0 g) obtained in Reference Example 18 to give 4-[2-(3,5-dichloro-4-pyridyl)-1-oxoethyl]-7-methoxy-2-(2-pyridyl)benzofuran (1.89 g, 63.4%) as a yellowish white solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 116.

Melting point: 226-227 °C
NMR(DMSO-d_6, δ, ppm): 4.14(s, 3H), 4.88(s, 2H), 7.24 (d, J=9Hz, 1H), 7.53(dd, J=5Hz, 7Hz, 1H), 8.0-8.1(m, 2H), 8.13(s, 1H), 8.34(d, J=9Hz, 1H), 8.70(s, 2H), 8.73(d, J=5Hz, 1H)
IR(KBr, cm^{-1}): 1670, 1605, 1580, 1310
MASS[FAB(pos.), m/e]: 417, 415, 413(M^+), 252

Elemental analysis: $C_{21}H_{14}N_2O_3Cl_2 \cdot 2HCl$			
Found (%)	C:51.71,	H:3.26,	N:5.62
Calcd.(%)	C:51.88,	H:3.32,	N:5.76

Example 117

7-Methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-2-(2-pyridyl)benzofuran • 2 hydrochloride (Compound 117)

Substantially the same procedure as in Example 98 was repeated using Compound IIr (4.0 g) obtained in Reference Example 18 to give 7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-2-(2-pyridyl)benzofuran (1.30 g, 26.6%) as a white solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 117.

Melting point: 218-220 °C
NMR(DMSO-d_6, δ, ppm): 4.13(s, 3H), 4.97(s, 2H), 7.23 (d, J=8Hz, 1H), 7.49(m, 1H), 8.0-8.1(m, 5H), 8.22(d, J=8Hz, 1H), 8.72(d, J=4Hz, 1H), 8.93(d, J=6Hz, 2H)
IR(KBr, cm^{-1}): 1670, 1610, 1470, 1305
MASS(m/e): 344(M^+), 252

Elemental analysis: $C_{21}H_{16}N_2O_3 \cdot 2.0HCl \cdot 0.6H_2O$			
Found (%)	C:58.86,	H:4.54,	N:6.47
Calcd.(%)	C:58.92,	H:4.52,	N:6.54

Example 118

7-Methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-3-phenylbenzofuran • hydrochloride (Compound 118)

Substantially the same procedure as in Example 98 was repeated using Compound IIv (0.60 g) obtained in Reference Example 22 to give 7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-3-phenylbenzofuran (0.25 g, 35%) as a white solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 118.

Melting point: 176-178 °C
NMR(DMSO-d_6, δ, ppm): 4.08(s, 3H), 4.77(s, 2H), 7.13-7.44(m, 6H), 7.80(d, J=6Hz, 1H), 7.98(d, J=8Hz, 1H), 8.21(s, 1H), 8.84(d, J=6Hz, 1H)
IR(KBr, cm^{-1}): 1674, 1618, 1402, 1304
MASS(m/e): 343(M^+)

Elemental analysis: $C_{22}H_{17}NO_3 \cdot HCl \cdot 0.5H_2O$			
Found (%)	C:67.85,	H:4.88,	N:3.52
Calcd.(%)	C:67.95,	H:4.92,	N:3.60

Example 119

4-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-3-ethoxycarbonylmethyl-7-methoxybenzofuran (Compound 119)

(Step A) (±)-4-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-3-ethoxycarbonyl-7-methoxybenzofuran (Compound 119a)

Substantially the same procedure as in Step A of Example 45 was repeated using Compound IIj (0.28 g) obtained in Reference Example 10 to give Compound 119A (0.31 g, 70%) as a pale-yellow solid.

Melting point: 133-135 °C
NMR($CDCl_3$, δ, ppm): 1.22(t, J=7Hz, 3H), 2.40(d, J=5Hz, 1H), 3.34(dd, J=4, 13Hz, 1H), 3.76(dd, J=10, 13Hz, 1H), 3.97(s, 2H), 4.02(s, 3H), 4.07-4.23(m, 2H), 5.30-5.46(m, 1H), 6.82(d, J=8Hz, 1H), 7.32 (d, J=8Hz, 1H), 7.64(s, 1H), 8.46 (s, 2H)

(Step B) (Compound 119)

Substantially the same procedure as in Example 95 was repeated using Compound 119A (0.30 g) obtained in Step A to give Compound 119 (0.28 g, 95%) as a white solid.

Melting point: 105-115 °C
NMR($CDCl_3$, δ, ppm): 1.16(t, J=7Hz, 3H), 3.88(s, 2H), 4.00-4.15(m, 5H), 4.69(s, 2H), 6.87(d, J=8Hz, 1H), 7.65(s, 1H), 7.95(d, J=8Hz, 1H), 8.51(s, 2H)

Example 120

3-Ethoxycarbonylmethyl-7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]benzofuran (Compound 120)

Compound 119 (0.04 g) obtained in Example 119 was dissolved in DMF-methanol (1:1) (1.0 ml), and 10% palladium carbon (0.016 g) was added thereto, followed by hydrogenation at normal temperature and normal pressure for 6 hours. The catalyst was removed and the filtrate was concentrated. Water and a saturated aqueous solution of sodium bicarbonate were added to the residue, and a precipitate was collected by filtration and dried to give Compound 120 (0.02 g, 9%) as a white solid.

Melting point: 111-117 °C
NMR($CDCl_3$, δ, ppm): 1.18(t, J=7Hz, 3H), 3.92(s, 2H), 4.03(q, J=7Hz, 2H), 4.07(s, 3H), 4.29(s, 2H), 6.82(d, J=9Hz, 1H), 7.22(d, J=6Hz, 2H), 7.69(s, 1H), 7.75(d, J=9Hz, 1H), 8.56(d, J=6Hz, 2H)

Example 121

5-(3,5-Dichloro-4-pyridylaminocarbonyl)-8-methoxy-2,2-dimethylbenzopyran (Compound 121)

Substantially the same procedure as in Example 1 was repeated using Compound IIao (0.432 g) obtained in Reference Example 41 to give Compound 121 (0.229 g, 33%) as a white solid.

Melting point: 174-178 °C
NMR($CDCl_3$, δ, ppm): 1.51(s, 6H), 3.92(s, 3H), 5.77(d, J=10Hz, 1H), 6.82(d, J=8.7Hz, 1H), 6.95(d, J=10Hz, 1H), 7.29(d, J=8.7Hz, 1H), 7.41-7.52(brs, 1H), 8.58(s, 2H)
MASS(m/e): 378(M^+)
IR(KBr, cm^{-1}): 1660, 1480, 1280

Elemental analysis: $C_{18}H_{16}N_2O_3Cl_2$			
Found (%)	C:57.12,	H:4.37,	N:7.23
Calcd.(%)	C:57.01,	H:4.25,	N:7.39

Example 122

5-(3,5-Dichloro-4-pyridylaminocarbonyl)-8-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran (Compound 122)

Substantially the same procedure as in Example 1 was repeated using Compound IIap (1.05 g) obtained in Reference Example 42 to give Compound 122 (0.94 g, 56%) as a white solid.

Melting point: 155-156 °C
NMR($CDCl_3$, δ, ppm): 1.42(s, 6H), 1.82(t, J=7.2Hz, 2H), 3.05(t, J=7.2Hz, 2H), 3.91(s, 3H), 6.79(d, J=8.3Hz, 1H), 7.28(d, J=8.3Hz, 1H), 7.38-7.59 (brs, 1H), 8.56(s, 2H)
MASS(m/e): 380(M^+)
IR(KBr, cm^{-1}): 1680, 1480, 1280

Elemental analysis: $C_{18}H_{18}N_2O_3Cl_2$			
Found (%)	C:56.71,	H:4.84,	N:7.22
Calcd.(%)	C:56.71,	H:4.76,	N:7.35

Example 123

5-(3,5-Dichloro-4-pyridylaminocarbonyl)-8-methoxy-spiro[benzopyran-2,1'-cyclopentane] (Compound 123)

Substantially the same procedure as in Example 1 was repeated using Compound IIaq (1.67 g) obtained in Reference Example 43 to give Compound 123 (1.44 g, 55%) as a white solid.

Melting point: 129-131 °C
NMR($CDCl_3$, δ, ppm): 1.50-2.32(m, 8H), 3.90(s, 3H), 5.82(d, J=9.0Hz, 1H), 6.80(d, J=8.2Hz, 1H), 6.99 (d, J=9.0Hz, 1H), 7.28(d, J=8.2Hz, 1H), 7.39-7.51(brs, 1H), 8.55(s, 2H)
MASS(m/e): 404(M^+)
IR(KBr, cm^{-1}): 1670, 1480, 1270

Elemental analysis: $C_{20}H_{18}N_2O_3Cl_2$			
Found (%)	C:59.13,	H:4.54,	N:6.66
Calcd.(%)	C:59.27,	H:4.48,	N:6.91

Example 124

8-Methoxy-5-(4-pyridylaminocarbonyl)-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane] • methanesulfonate (Compound 124)

Substantially the same procedure as in Example 6 was repeated using Compound IIas (0.96 g) obtained in Reference Example 45 to give 8-methoxy-5-(4-pyridylaminocarbonyl)-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane] (1.14 g, 92%) as a white solid. Then, substantially the same procedure as in Example 50 was repeated using the obtained solid to give Compound 124.

Melting point: 231-233 °C
NMR(DMSO, δ, ppm): 1.45-1.93(m, 10H), 2.30(s, 3H), 2.92(t, J=5Hz, 2H), 3.80(s, 3H), 6.94(d, J=8Hz, 1H), 7.21(d, J=8Hz, 1H), 8.20(d, J=7Hz, 2H), 8.72(d, J=7Hz, 2H), 11.4(s, 1H)
IR(KBr, cm^{-1}): 1690, 1510, 1270

Elemental analysis: $C_{20}H_{22}N_2O_3 \cdot CH_3SO_3H \cdot 0.1H_2O$			
Found (%)	C:57.78,	H:6.10,	N:6.15
Calcd.(%)	C:57.81,	H:6.05,	N:6.42

Example 125

8-Methoxy-5-[2-(4-pyridyl)ethenyl]-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane] • hydrochloride (Compound 125)

(Step A) 5-[1-Hydroxy-2-(4-pyridyl)ethyl]-8-methoxy-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane] (Compound 125a)

Compound 127 (0.78 g) obtained in Example 127 was dissolved in methanol (8 ml) and sodium borohydride (0.18 g) was added thereto under ice-cooling, followed by stirring at room temperature for 2 hours. The mixture was cooled again with ice and dilute hydrochloric acid was dropwise added thereto. After the solvent was distilled off, water was added to the residue, and the mixture was extracted with ethyl acetate and washed with a saturated saline. The resultant was dried over sodium sulfate and the solvent was distilled off to give Compound 125a (0.63 g, 80%) as white crystals.

Melting point: 153-156 °C
NMR($CDCl_3$, δ, ppm): 1.36-2.07(m, 10H), 2.30-2.50(m, 1H), 2.70-3.10(m, 3H), 3.83(s, 3H), 4.99-5.10(m, 1H), 6.78(d, J=8.2Hz, 1H), 7.02(d, J=8.2Hz, 1H), 7.08(d, J=6.8Hz, 2H), 8.46(d, J=6.8Hz, 2H)
MASS(m/e): 339(M^+)

(Step B) (Compound 125)

Substantially the same procedure as in Example 67 was repeated using Compound 125a (0.58 g) obtained in Step A to give 8-methoxy-5-[2-(4-pyridyl)ethenyl]-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane] (0.355 g, 65%) as a yellow solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained solid to give Compound 125.

Melting point: 208-215 °C
NMR($CDCl_3$, δ, ppm): 1.49-1.99(m, 10H), 2.95(t, J=6.8Hz, 2H), 3.90(s, 3H), 6.80 (d, J=8.5Hz, 1H), 7.00(d, J=15Hz, 1H), 7.29(d, J=8.5Hz, 1H), 7.70-7.90(m, 3H), 8.50-8.67(m, 2H)
IR(KBr, cm^{-1}): 1620, 1580, 1500

Elemental analysis: $C_{21}H_{23}NO_3 \cdot HCl \cdot 0.2H_2O$			
Found (%)	C:69.75,	H:6.74,	N:3.82
Calcd.(%)	C:69.78,	H:6.80,	N:3.87

Example 126

8-Methoxy-5-[2-(4-pyridyl)ethenyl]-spiro[3,4-dihydrobenzopyran-2,1'-cyclohexane] • hydrochloride (Compound 126)

(Step A) 5-[1-Hydroxy-2-(4-pyridyl)ethyl]-8-methoxy-spiro[3,4-dihydrobenzopyran-2,1'-cyclohexane] (Compound 126a)

Substantially the same procedure as in Step A of Example 125 was repeated using Compound 128 (0.73 g)

obtained in Example 128 to give Compound 126a (0.47 g, 64%) as a white solid.

Melting point: 123-133 °C
NMR($CDCl_3$, δ, ppm): 1.20-1.90(m, 12H), 2.29-2.45(m, 1H), 2.68-3.15(m, 3H), 3.86(s, 3H), 4.98-5.12(m, 1H), 6.78(d, J=9Hz, 1H), 7.01(d, J=9Hz, 1H), 7.08 (d, J=6Hz, 2H), 8.47(d, J=6Hz, 2H)

(Step B) (Compound 126)

Substantially the same procedure as in Example 67 was repeated using Compound 126a (0.48 g) obtained in Step A to give 8-methoxy-5-[2-(4-pyridyl)ethenyl]-spiro[3,4-dihydrobenzopyran-2,1'-cyclohexane] (0.14 g, 31%) as yellow crystals. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 126.

Melting point: 222-230 °C
NMR($CDCl_3$, δ, ppm): 1.25-2.00(m, 12H), 2.90(t, J=7Hz, 2H), 3.92(s, 3H), 6.80 (d, J=9Hz, 1H), 6.97(d, J=16Hz, 1H), 7.75-7.90(m, 4H), 8.59(d, J=6Hz, 2H)

Elemental analysis: $C_{22}H_{25}NO_2 \cdot HCl \cdot 0.1H_2O$			
Found (%)	C:70.68,	H:7.04,	N:3.65
Calcd.(%)	C:70.71,	H:7.07,	N:3.75

Example 127

8-Methoxy-5-[1-oxo-2-(4-pyridyl)ethyl]-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane] • hydrochloride (Compound 127)

Substantially the same procedure as in Example 98 was repeated using Compound IIar (1.83 g) obtained in Reference Example 44 to give 8-methoxy-5-[1-oxo-2-(4-pyridyl)ethyl]-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane] (1.61 g, 72%) as a pale-yellow solid. Then, substantially the same procedure as in Example 51 was repeated using the obtained solid to give Compound 127.

Melting point: 186-192 °C
NMR($CDCl_3$, δ, ppm): 1.50-2.07(m, 10H), 3.06(t, J=6.8Hz, 2H), 3.91(s, 3H), 4.59(s, 2H), 6.80(d, J=8.5Hz, 1H), 7.52(d, J=8.5Hz, 1H), 7.88(d, J=6.7Hz, 2H), 8.72(d, J=6.7Hz, 2H)
IR(KBr, cm^{-1}): 1670, 1560, 1280

Elemental analysis: $C_{21}H_{23}NO_3 \cdot HCl \cdot 0.4H_2O$			
Found (%)	C:66.19,	H:6.75,	N:3.72
Calcd.(%)	C:66.19,	H:6.56,	N:3.68

Example 128

8-Methoxy-5-[1-oxo-2-(4-pyridyl)ethyl]-spiro[3,4-dihydrobenzopyran-2,1'-cyclohexane] • hydrochloride

Substantially the same procedure as in Example 98 was repeated using Compound IIat (2.1 g) obtained in Reference Example 46 to give 8-methoxy-5-[1-oxo-2-(4-pyridyl)ethyl]-spiro[3,4-dihydrobenzopyran-2,1'-cyclohexane] (1.2 g, 48%) as pale-yellow crystals. Then, substantially the same procedure as in Example 51 was repeated using the

obtained crystals to give Compound 128.

Melting point: 185-194 °C
NMR($CDCl_3$, δ, ppm): 1.25-1.90(m, 12H), 3.01(t, J=7Hz, 2H), 3.95(s, 3H), 4.56(s, 2H), 6.82(d, J=9Hz, 1H), 7.51(d, J=9Hz, 1H), 7.82(d, J=6Hz, 2H), 8.71(d, J=6Hz, 2H)

Elemental analysis: $C_{22}H_{25}NO_3 \cdot HCl \cdot 0.6H_2O$			
Found (%)	C:66.34,	H:6.84,	N:3.45
Calcd.(%)	C:66.27,	H:6.88,	N:3.51

Example 129

7-(3,5-Dichloro-4-pyridylaminocarbonyl)-4-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 129)

Substantially the same procedure as in Example 1 was repeated using Compound IIav (1.00 g) obtained in Reference Example 48 to give Compound 129 (1.33 g, 84%) as pale-yellow crystals.

Melting point: 156-158 °C
NMR($CDCl_3$, δ, ppm): 1.80-2.29(m, 8H), 3.20(s, 2H), 3.91(s, 3H), 6.58(d, J=9Hz, 1H), 7.99(d, J=9Hz, 1H), 8.54(s, 2H), 9.42(s, 1H)
IR(KBr, cm^{-1}): 1690, 1552, 1495, 1271
MASS(m/e): 392(M^+)

Elemental analysis: $C_{19}H_{18}N_2O_3Cl_2$			
Found (%)	C:58.06,	H:4.56,	N:6.94
Calcd.(%)	C:58.03,	H:4.61,	N:7.12

Example 130

4-Methoxy-7-(4-pyridylaminocarbonyl)-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] • methanesulfonate (Compound 130)

Substantially the same procedure as in Example 6 was repeated using Compound IIav (1.00 g) obtained in Reference Example 48 to give 4-methoxy-7-(4-pyridylaminocarbonyl)-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (0.88 g, 63%) as pale-yellow crystals. Then, substantially the same procedure as in Example 50 was repeated using the obtained crystals to give Compound 130.

Melting point: 164 °C (decomposed)
NMR(DMSO-d_6, δ, ppm): 1.75-1.88(m, 6H), 2.10-2.22(m, 2H), 2.31(s, 3H), 3.18(s, 2H), 3.89(s, 3H), 6.76 (d, J=9Hz, 1H), 7.72(d, J=9Hz, 1H), 8.13(d, J=7Hz, 1H), 8.75(d, J=7Hz, 1H), 10.5(s, 1H)
IR(KBr, cm^{-1}): 1693, 1612, 1512, 1267
MASS(m/e): 324(M^+)

Elemental analysis: $C_{19}H_{20}N_2O_3 \cdot CH_3SO_3H \cdot 0.3H_2O$			
Found (%)	C:56.45,	H:5.78,	N:6.52
Calcd.(%)	C:58.41,	H:5.82,	N:6.58

Example 131

7-[2-(3,5-Dichloro-4-pyridyl)ethenyl]-4-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 131)

(Step A) 7-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-4-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 131a)

Substantially the same procedure as in Step A of Example 45 was repeated using Compound IIau (1.00 g) obtained in Reference Example 47 to give Compound 131a (1.32 g, 78%) as pale-yellow crystals.

NMR($CDCl_3$, δ, ppm): 1.70-2.20(m, 8H), 2.91(d, J=9Hz, 1H), 3.11(s, 2H), 3.25(dd, J=5, 13Hz, 1H), 3.61 (dd, J=9, 13Hz, 1H), 3.82(s, 3H), 4.94-5.03(m, 1H), 6.35(d, J=9Hz, 1H), 6.98(d, J=9Hz, 1H), 8.43(s, 1H)
MASS(m/e): 393(M^+)

(Step B) (Compound 131)

Substantially the same procedure as in Example 67 was repeated using Compound 131a (0.66 g) obtained in Step A to give Compound 131 (0.55 g, 87%) as yellow crystals.

Melting point: 99-101 °C
NMR($CDCl_3$, δ, ppm): 1.65-2.20(m, 8H), 3.11(s, 2H), 3.82(s, 3H), 6.38(d, J=9Hz, 1H), 7.13(d, J=9Hz, 1H), 7.45(d, J=17Hz, 1H), 7.50(d, J=17Hz, 1H), 8.43(s, 2H)
IR(KBr, cm^{-1}): 1612, 1556, 1500, 1232
MASS(m/e): 375(M^+)

Elemental analysis: $C_{20}H_{19}NO_2Cl_2$			
Found (%)	C:64.14,	H:5.19,	N:3.57
Calcd.(%)	C:63.84,	H:5.09,	N:3.72

Example 132

7-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-4-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 132)

Substantially the same procedure as in Example 95 was repeated using Compound 131a (0.66 g) obtained in Step A in Example 131 to give Compound 132 (0.23 g, 35%) as white crystals.

Melting point: 70-72 °C
NMR($CDCl_3$, δ, ppm): 1.78-2.24(m, 8H), 3.16(s, 2H), 3.90(s, 3H), 4.63(s, 2H), 6.51(d, J=9Hz, 1H), 7.82(d, J=9Hz, 1H), 8.49(s, 2H)
IR(KBr, cm^{-1}): 1668, 1427, 1297, 1093
MASS(m/e): 391(M^+)

Elemental analysis: $C_{20}H_{19}NO_3Cl_2$			
Found (%)	C:61.30,	H:4.84,	N:3.41
Calcd.(%)	C:61.24,	H:4.88,	N:3.57

Example 133

4-Methoxy-7-[1-oxo-2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 133)

Substantially the same procedure as in Example 98 was repeated using Compound IIaw (0.86 g) obtained in Reference Example 49 to give Compound 133 (0.42 g, 40%) as white crystals.

Melting point: 101-103 °C
NMR($CDCl_3$, δ, ppm): 1.73-2.17(m, 8H), 3.11(s, 2H), 3.88(s, 3H), 4.26(s, 2H), 6.49(d, J=9Hz, 1H), 7.17-7.19(m, 2H), 7.81(d, J=9Hz, 1H), 8.50-8.53 (m, 2H)
IR(KBr, cm^{-1}): 1680, 1612, 1430, 1248
MASS(m/e): 323(M^+)

Elemental analysis: $C_{20}H_{21}NO_3$			
Found (%)	C:74.63,	H:6.68,	N:4.26
Calcd.(%)	C:74.28,	H:6.54,	N:4.33

Example 134

7-(3,5-Dichloro-4-pyridylaminocarbonyl)-4-methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane] (Compound 134)

Substantially the same procedure as in Example 1 was repeated using Compound IIaz (0.70 g) obtained in Reference Example 52 to give Compound 134 (0.73 g, 66%) as white crystals.

Melting point: 168-170 °C
NMR($CDCl_3$, δ, ppm): 1.84-1.96(m, 4H), 2.24-2.31(m, 4H), 3.97(s, 3H), 6.67(d, J=9Hz, 1H), 7.60(d, J=9Hz, 1H), 8.55(s, 2H), 8.78(s, 1H)
IR(KBr, cm^{-1}): 1689, 1641, 1490, 1286
MASS(m/e): 394(M^+)

Elemental analysis: $C_{18}H_{16}N_2O_4Cl_2$			
Found (%)	C:54.57,	H:4.05,	N:6.95
Calcd.(%)	C:54.70,	H:4.08,	N:7.09

Example 135

4-Methoxy-7-(4-pyridylaminocarbonyl)-spiro[1,3-benzodioxole-2,1'-cyclopentane] • methanesulfonate (Compound 135)

Substantially the same procedure as in Example 6 was repeated using Compound IIaz (0.84 g) obtained in Refer-

ence Example 52 to give 4-methoxy-7-(4-pyridylaminocarbonyl)-spiro[1,3-benzodioxole-2,1'-cyclopentane] (0.34 g, 31%) as pale-yellow crystals. Then, substantially the same procedure as in Example 50 was repeated using the obtained crystals to give Compound 135.

Melting point: 133-134 °C
NMR(DMSO-d_6, δ, ppm): 1.77-1.83(m, 4H), 2.06-2.22(m, 4H), 2.31(s, 3H), 3.90(s, 3H), 6.84(d, J=9Hz, 1H), 7.36(d, J=9Hz, 1H), 8.18(d, J=7Hz, 2H), 8.73(d, J=7Hz, 2H), 10.9(s, 1H)
IR(KBr, cm^{-1}): 1637, 1508, 1280, 1120
MASS(m/e): 326(M^+)

Elemental analysis: $C_{18}H_{18}N_2O_4 \cdot CH_3SO_3H \cdot 0.3H_2O$			
Found (%)	C:53.34,	H:5.20,	N:6.58
Calcd.(%)	C:53.34,	H:5.32,	N:6.55

Example 136

4-Methoxy-7-[2-(4-pyridyl)ethyl]-spiro[1,3-benzodioxole-2,1'-cyclopentane] • hydrochloride (Compound 136)

Substantially the same procedure as in Example 120 was repeated using Compound 138 (0.86 g) obtained in Example 138 to give 4-methoxy-7-[2-(4-pyridyl)ethyl]-spiro[1,3-benzodioxole-2,1'-cyclopentane] (0.078 g, 99%) as pale-yellow crystals. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 136.

Melting point: 160-162 °C
NMR(DMSO-d_6, δ, ppm): 1.71-2.01(m, 8H), 2.89(t, J=7Hz, 2H), 3.15(t, J=7Hz, 2H), 3.75(s, 3H), 6.51(d, J=9Hz, 1H), 6.61(d, J=9Hz, 1H), 7.83(d, J=6Hz, 2H), 8.79(d, J=6Hz, 2H)
IR(KBr, cm^{-1}): 1640, 1508, 1456, 1333
MASS(m/e): 311(M^+)

Elemental analysis: $C_{19}H_{21}NO_3 \cdot HCl \cdot 0.2H_2O$			
Found (%)	C:64.82,	H:6.35,	N:3.82
Calcd.(%)	C:64.93,	H:6.42,	N:3.99

Example 137

4-Methoxy-7-[1-phenyl-2-(4-pyridyl)ethyl]-spiro[1,3-benzodioxole-2,1'-cyclopentane] • hydrochloride (Compound 137)

Substantially the same procedure as in Example 120 was repeated using Compound 139 (0.76 g) obtained in Example 139 to give 4-methoxy-7-[1-phenyl-2-(4-pyridyl)ethyl]-spiro[1,3-benzodioxole-2,1'-cyclopentane] (0.75 g, 98%) as a pale-yellow oily substance. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 137.

Melting point: 179-182 °C
NMR(DMSO-d_6, δ, ppm): 1.75-2.00(m, 8H), 3.64-3.71(m, 2H), 3.72(s, 3H), 4.48(t, J=8Hz, 1H), 6.51(d, J=9Hz, 1H), 6.76(d, J=9Hz, 1H), 7.16-7.38(m, 5H), 7.84(d, J=5Hz, 2H), 8.75(d, J=5Hz, 2H)
IR(KBr, cm^{-1}): 1645, 1633, 1504
MASS(m/e): 387(M^+)

Elemental analysis: $C_{25}H_{25}NO_3 \cdot HCl \cdot 0.3H_2O$			
Found (%)	C:70.07,	H:6.23,	N:3.17
Calcd.(%)	C:69.94,	H:6.24,	N:3.26

Example 138

7-[2-(3,5-Dichloro-4-pyridyl)ethenyl]-4-methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane] (Compound 138)

(Step A) 7-[2-(3,5-Dichloro-4-pyridyl)-1-hydroxyethyl]-4-methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane] (Compound 138a)

Substantially the same procedure as in Step A of Example 45 was repeated using Compound IIax (0.47 g) obtained in Reference Example 50 to give Compound 138a (0.73 g, 92%) as pale-yellow crystals.

NMR($CDCl_3$, δ, ppm): 1.75-2.15(m, 8H), 3.09(d, J=6Hz, 1H), 3.31(dd, J=6, 13Hz, 1H), 3.51(dd, J=9, 13Hz, 1H), 3.87(s, 3H), 5.09-5.15(m, 1H), 6.46(d, J=9Hz, 1H), 6.79(d, J=9Hz, 1H), 8.34(s, 2H)
MASS(m/e): 395(M^+)

(Step B) (Compound 138)

Substantially the same procedure as in Example 67 was repeated using Compound 138a (0.74 g) obtained in Step A to give Compound 138 (0.59 g, 80%) as yellow crystals.

Melting point: 100-101 °C
NMR($CDCl_3$, δ, ppm): 1.82-1.94(m, 4H), 2.14-2.26(m, 4H), 3.91(s, 3H), 6.51(d, J=9Hz, 1H), 6.87(d, J=9Hz, 1H), 7.30(d, J=16Hz, 1H), 7.42(d, J=16Hz, 1H), 8.45(s, 2H)
IR(KBr, cm^{-1}): 1618, 1452, 1288, 1113
MASS(m/e): 377(M^+)

Elemental analysis: $C_{19}H_{17}NO_3Cl_2$			
Found (%)	C:60.39,	H:4.49,	N:3.65
Calcd.(%)	C:60.33,	H:4.53,	N:3.70

Example 139

4-Methoxy-7-[1-phenyl-2-(4-pyridyl)ethenyl]-spiro[1,3-benzodioxole-2,1'-cyclopentane] (Compound 139)

(Step A) 7-[1-Hydroxy-1-phenyl-2-(4-pyridyl)ethyl]-4-methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane] (Compound 139a)

Substantially the same procedure as in Step A of Example 47 was repeated using Compound IIba (4.90 g) obtained in Reference Example 53 to give Compound 139 (5.34 g, 84%) as pale-yellow crystals.

NMR($CDCl_3$, δ, ppm): 1.69-2.10(m, 8H), 3.10 (s, 1H), 3.46(d, J=12Hz, 1H), 3.69(d, J=12Hz, 1H), 3.87(s, 3H), 6.44(d, J=9Hz, 1H), 6.71(d, J=9Hz, 1H), 6.93(d, J=6Hz, 2H), 7.22-7.39(m, 5H), 8.37(d, J=6Hz, 2H)
MASS(m/e): 403(M^+)

(Step B) (Compound 139) (an E/Z mixture)

Substantially the same procedure as in Example 67 was repeated using Compound 139a (2.0 g) obtained in Step A to give Compound 139 (0.76 g, 40%) as pale-yellow crystals.

NMR($CDCl_3$, δ, ppm): 0.83-2.22(m, 8H), 3.88(s, 3H x 0.75), 3.92(s, 3H x 0.25), 6.39(s, 2H x 0.75), 6.49-6.53(m, 2H x 0.25), 6.79(d, J=6Hz, 2H x 0.75), 6.88(s, 1H x 0.25), 7.00(d, J=6Hz, 2H x 0.25), 7.20(s, 1H x 0.75), 7.15-7.38(m, 5H), 8.31(d, J=6Hz, 2H x 0.75), 8.40(d, J=6Hz, 2H x 0.25)
MASS(m/e): 385(M^+)

Example 140

7-[2-(3,5-Dichloro-4-pyridyl)-1-oxoethyl]-4-methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane] (Compound 140)

Substantially the same procedure as in Example 95 was repeated using Compound 138a (1.50 g) obtained in Step A of Example 138 to give Compound 140 (0.77 g, 52%) as white crystals.

Melting point: 110-112 °C
NMR($CDCl_3$, δ, ppm): 1.83-1.96(m, 4H), 2.18-2.28(m, 4H), 3.97(s, 3H), 4.59(s, 2H), 6.61(d, J=9Hz, 1H), 7.47(d, J=9Hz, 1H), 8.50(s, 2H)
IR(KBr, cm^{-1}): 1633, 1448, 1286, 1263
MASS(m/e): 393(M^+)

Elemental analysis: $C_{19}H_{17}NO_4Cl_2$			
Found (%)	C:58.05,	H:4.32,	N:3.52
Calcd.(%)	C:57.88,	H:4.35,	N:3.55

Example 141

4-Methoxy-7-[1-oxo-2-(4-pyridyl)ethyl]-spiro[1,3-benzodioxole-2,1'-cyclopentane] • hydrochloride (Compound 141)

Substantially the same procedure as in Example 98 was repeated using Compound IIay (1.0 g) obtained in Reference Example 51 to give 4-methoxy-7-[1-oxo-2-(4-pyridyl)ethyl]-spiro[1,3-benzodioxole-2,1'-cyclopentane] (0.33 g, 27%) as white crystals. Then, substantially the same procedure as in Example 51 was repeated using the obtained crystals to give Compound 141.

Melting point: 110-111 °C
NMR($CDCl_3$, δ, ppm): 1.75-1.88(m, 4H), 2.18-2.28(m, 4H), 3.90(s, 3H), 4.62(s, 2H), 6.82(d, J=9Hz, 1H), 7.38(d, J=9Hz, 1H), 7.92(d, J=5Hz, 2H), 8.84(d, J=5Hz, 2H)
IR(KBr, cm^{-1}): 1668, 1633, 1446, 1119

Example 142

7-Methoxy-4-[2-(4-pyridyl)ethynyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 142)

(Step A) 6-Bromo-4-[1,2-dibromo-2-(4-pyridyl)ethyl]-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 142a)

Bromine (0.1 ml) was dropwise added to a solution of (E)-7-methoxy-4-[2-(4-pyridyl)ethenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (0.18 g) obtained in Example 74 in dichloromethane (15 ml) at 0°C, followed by stirring at the same temperature for 30 minutes. Water was added to the reaction solution and the mixture was extracted with chloroform. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to give Compound 142a (0.26 g, 81.2%) as pale-yellow crystals.

NMR($DMSO-d_6$, δ, ppm): 1.50-2.15(m, 8H), 3.24(d, J=15.3Hz, 1H), 3.65(d, J= 15.8Hz, 1H), 3.82(s, 3H), 5.90(d, J=11.8Hz, 1H), 6.15(d, J=12.3Hz, 1H), 7.13(s, 1H), 7.67(d, J=5.9Hz, 2H), 8.69(d, J=5.4Hz, 2H)

(Step B) 6-Bromo-7-methoxy-4-[2-(4-pyridyl)ethynyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 142b)

Potassium tert-butoxide (0.15 g) was added to a solution of Compound 142a (0.25 g) obtained in Step A in THF (9 ml) at 0°C, followed by stirring at room temperature for 5 hours. The reaction solution was poured into water and the mixture was extracted with diethyl ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/1) to give Compound 142b (0.12 g, 68.2%) as pale-yellow crystals.

NMR($DMSO-d_6$, δ, ppm): 1.70-1.95(m, 6H), 2.05-2.25(m, 2H), 3.32(s, 2H), 3.88(s, 3H), 6.97(s, 1H), 7.39 (d, J=5.4Hz, 2H), 8.60(d, J=5.4Hz, 2H)
MASS(m/e): 383, 385(M^+)

(Step C) (Compound 142)

Under an argon atmosphere, a solution (2.6 ml) of Compound 142b (0.1 g) obtained in Step B in THF was cooled to -78°C, and then a 1.7M solution (0.2 ml) of n-butyl lithium in hexane was dropwise added thereto, followed by stirring at the same temperature for one hour. The reaction solution was adjusted to pH 7 by adding droppwise 1N hydrochloric acid, followed by stirring at room temperature for one hour. A small amount of water was added to the reaction solution and the mixture was extracted with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/2) to give Compound 142 (0.014 g, 17.4 %) as pale-yellow crystals.

Melting point: 128-131 °C
NMR($DMSO-d_6$, δ, ppm): 1.42(s, 6H), 3.15(s, 2H), 3.80 (s, 3H), 3.87(s, 3H), 6.94(s, 2H), 7.62(d, J=8.4Hz, 2H), 7.99(d, J=8.4Hz, 2H)
IR(KBr, cm^{-1}): 2216, 1589, 1506
MASS(m/e): 305(M^+)

Example 143

7-Methoxy-4-[1-oxo-2-(N-oxo-4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 143)

m-Chloroperbenzoic acid (0.72 g) was added to a solution of 7-methoxy-4-[1-oxo-2-(4-pyridyl)ethyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (0.27 g) obtained in Example 100 in dichloromethane (8.3 ml) at 0°C, followed by stirring at room temperature for 5 hours. A saturated aqueous solution of sodium bicarbonate was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 15/1) to give Compound 143 (0.07 g, 24.8 %) as pale-yellow crystals.

NMR($DMSO-d_6$, δ, ppm): 1.72-1.91(m, 6H), 2.10-2.16(m, 2H), 3.51(s, 2H), 3.95(s, 3H), 4.24(s, 2H), 6.81 (d, J=8.6Hz, 2H), 7.18(d, J=6.9Hz, 2H), 7.45(d, J=8.6Hz, 1H), 8.20(d, J=6.9Hz, 2H)
MASS(m/e): 339(M^+)

Example 144

7-Methoxy-4-[4-(methoxycarbonyl)phenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 144)

(Step A) 7-Methoxy-4-tributylstannyl-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 144a)

Under an argon atmosphere, a solution (80 ml) of Compound IIa-c (2.0 g) obtained in Step C of Reference Example 1 in THF was cooled to -78°C, and then a solution (5.0 ml) of 1.70M butyl lithium in hexane was dropwise added thereto, followed by stirring at the same temperature for one hour. Tributyltin chloride (2.1 ml) was dropwise added to the mix-

ture, followed by stirring at room temperature for 2 hours and then at 60°C for one hour. The solvent was distilled off and the residue was dried under reduced pressure to give a crude desired product. This product was immediately subjected to a subsequent step without being purified.

(Step B) (Compound 144)

A solution (30 ml) of Compound 144a obtained in Step A in DMF was added to a mixture of methyl 4-bromobenzoate (1.67 g), palladium acetate (0.18 g), sodium carbonate (2.10 g), and dimethylformamide (DMF) (70 ml), followed by stirring at 80°C for one hour. A small amount of water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20) to give Compound 144 (1.35 g, 55.6%) as colorless crystals.

Melting point: 116-122 °C
NMR(DMSO-d_6, δ, ppm): 1.42(s, 6H), 3.15(s, 2H), 3.80 (s, 3H), 3.87(s, 3H), 6.94(s, 2H), 7.62(d, J=8.4Hz, 2H), 7.99(d, J=8.4Hz, 2H)
IR(KBr, cm^{-1}): 1720, 1606
MASS(m/e): 312(M^+)

Elemental analysis: $C_{19}H_{20}O_4$			
Found (%)	C:73.19,	H:6.58,	N:0.12
Calcd.(%)	C:73.06,	H:6.45,	N:0.00

Example 145

4-(4-Carboxyphenyl)-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 145)

A mixture of Compound 144 (1.0 g) obtained in Example 144, a 4N aqueous solution (8.0 ml) of sodium hydroxide, and ethanol (40 ml) was stirred at room temperature for 4 hours. The solvent was removed and the residue was dissolved in water. Concentrated hydrochloric acid was dropwise added to the solution, and the generated precipitate was collected by filtration, washed with water, and dried to give Compound 145 (0.82 g, 85.9%) as white crystals.

Melting point: 249-252 °C
NMR(DMSO-d_6, δ, ppm): 1.42(s, 6H), 3.15(s, 2H), 3.80 (s, 3H), 6.94(s, 2H), 7.59(d, J=8.4Hz, 2H), 7.98 (d, J=7.9Hz, 2H), 12.94(brs, 1H)
IR(KBr, cm^{-1}): 1681, 1606
MASS(m/e): 298(M^+)

Elemental analysis: $C_{18}H_{18}O_4$			
Found (%)	C:72.51,	H:6.18,	N:0.15
Calcd.(%)	C:72.47,	H:6.08,	N:0.00

Example 146

7-Methoxy-4-[3-(methoxycarbonyl)phenyl]-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 146)

A solution (30 ml) of Compound 144a obtained in Step A of Example 144 in DMF was added to a mixture of methyl 4-bromobenzoate (1.67 g), palladium acetate (0.18 g), sodium carbonate (2.10 g), and dimethylformamide (DMF) (70

ml), followed by stirring at 80°C for one hour. A small amount of water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid and a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/20) to give Compound 146 (1.69 g, 69.5%) as pale-yellow crystals.

Melting point: 89-91 °C
NMR(DMSO-d_6, δ, ppm): 1.42(s, 6H), 3.12(s, 2H), 3.80 (s, 3H), 3.88(s, 3H), 6.90(d, J=8.4Hz, 1H), 6.95 (d, J=8.4Hz, 1H), 7.58(dd, J=7.4Hz, 1H), 7.76(dd, J=7.9, 1.5Hz, 1H), 7.91(d, J=7.4Hz, 1H), 7.99(d, J=1.5Hz, 1H)
IR(KBr, cm^{-1}): 1716
MASS(m/e): 312(M^+)

Example 147

4-(3-Carboxyphenyl)-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound 147)

A mixture of Compound 146 (1.3 g) obtained in Example 146, a 4N aqueous solution (10.4 ml) of sodium hydroxide, and ethanol (50 ml) was stirred at room temperature for 3 hours. The solvent was removed and the residue was dissolved in water. Concentrated hydrochloric acid was dropwise added to the solution, and the generated precipitate was collected by filtration, washed with water, and dried to give Compound 147 (1.15 g, 92.7%) as white crystals.

Melting point: 220-225 °C
NMR(DMSO-d_6, δ, ppm): 1.42(s, 6H), 3.12(s, 2H), 3.79 (s, 3H), 6.90(d, J=8.4Hz, 1H), 6.95(d, J=8.4Hz, 1H), 7.55(dd, J=7.4Hz, 1H), 7.72(dd, J=6.4, 1.5Hz, 1H), 7.89(dd, J=6.4, 1.5Hz, 1H), 7.97(d, J=1.5Hz, 1H), 13.17(brs, 1H)
IR(KBr, cm^{-1}): 1683
MASS(m/e): 298(M^+)

Elemental analysis: $C_{18}H_{18}O_4$			
Found (%)	C:72.21,	H:6.02,	N:0.05
Calcd.(%)	C:72.47,	H:6.08,	N:0.00

Reference Example 1

7-Methoxy-2,2-dimethyl-2,3-dihydrobenzofuran-4-carbaldehyde] (Compound IIa)

(Step A) 2-(2-Methyl-2-propen-1-yloxy)-4-bromoanisole (Compound IIa-a)

A mixture of 5-bromo-2-methoxyphenol (17.8 g), 3-chloro-2-methyl-1-propene (13.0 ml), potassium carbonate (18.2 g), and DMF (150 ml) was stirred at 80°C for 2 hours. The mixture was diluted with toluene, washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off to give Compound IIa-a (22.2 g, 98.4%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 1.76(s, 3H), 3.76(s, 3H), 4.48 (s, 2H), 4.96(s, 1H), 5.05(s, 1H), 6.92(d, J=8.41Hz, 1H), 7.04-7.11(m, 2H)

(Step B) 3-Bromo-6-methoxy-2-(2-methyl-2-propen-1-yl)phenol (Compound IIa-b)

Compound IIa-a (22.2 g) obtained in Step A was dissolved in 1-methylpyrrolidinone (50 ml) followed by stirring at 180°C for 5 hours. The mixture was extracted with ethyl acetate, washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (chloroform) to give Compound IIa-b (19.6 g, 88.5%) as a colorless oily substance.

NMR(DMSO-d_6, δ, ppm): 1.74(s, 3H), 3.37(s, 2H), 3.79 (s, 3H), 4.31(s, 1H), 4.68(s, 1H), 6.81(d, J=8.58Hz, 1H),

7.00(d, J=8.91Hz, 1H)

(Step C) 4-Bromo-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound IIa-c)

Compound IIa-b (19.6 g) obtained in Step B was dissolved in 88% formic acid (80 ml) followed by stirring at room temperature for 24 hours. The mixture was neutralized with an aqueous solution of sodium bicarbonate and extracted with toluene. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (chloroform) to give Compound IIa-c (16.3 g, 83.3%) as an oily substance.

NMR(DMSO-d_6, δ, ppm): 1.43(s, 6H), 2.99(s, 2H), 3.74 (s, 3H), 6.79(d, J=8.58Hz, 1H), 6.93(d, J=8.57Hz, 1H)
MASS(m/z): 258, 256(M^+)

(Step D) (Compound IIa)

Under an argon atmosphere, a solution (300 ml) of Compound IIa-c (20.0 g) obtained in Step C in THF was cooled to -78°C, and then a 1.69M solution (50.6 ml) of butyl lithium in hexane was dropwise added thereto. The reaction solution was gradually warmed and stirred at -20°C for one hour, and then DMF (200 ml) was dropwise added thereto, followed by stirring at room temperature for 2 hours. A Small amount of water was added to the reaction solution and the mixture was extractied with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/hexane = 9/1) to give Compound IIa (7.11 g, 44.3%) as colorless crystals.

NMR(DMSO-d_6, δ, ppm): 1.41(s, 6H), 3.28(s, 2H), 3.84 (s, 3H), 7.04(d, J=8.25Hz, 1H), 7.39(d, J=8.24Hz, 1H), 9.85(s, 1H)
MASS(m/z): 206, 191

Reference Example 2

2,2-Diethyl-7-methoxy-2,3-dihydrobenzofuran-4-carbaldehyde] (Compound IIb)

(Step A) 4-Bromo-2-(3-oxopentan-2-yloxy)anisole (Compound IIb-a)

A mixture of 5-bromo-2-methoxyphenol (50.0 g), 2-bromo-3-pentanone (68.1 g), potassium carbonate (52.8 g), and DMF (500 ml) was stirred at 70°C for 2 hours. After being allowed to stand for cooling, water was added to the mixture followed by extraction with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane:chloroform = 1:1) to give Compound IIb-a (86.8 g, 94.0%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 0.93(t, J=7.4Hz, 3H), 1.39(d, J=6.9Hz, 3H), 2.47-2.75(m, 2H), 3.77(s, 3H), 4.92(q, J=6.9Hz, 1H), 6.96(d, J=8.9Hz, 1H), 7.00 (d, J=2.7Hz, 1H), 7.10(dd, J=8.9, 2.5Hz, 1H)
MASS(m/e): 287(M^+), 285

(Step B) 4-Bromo-2-(3-methylenepentan-2-yloxy)anisole (Compound IIb-b)

Methyltriphenylphosphonium bromide (308.1 g) was suspended in THF (1 ℓ), and potassium t-butoxide (92.4 g) was added thereto under ice-cooling, followed by stirring for one hour under ice-cololing. A solution of Compound IIb-a (86.0 g) obtained in Step A in THF (500 ml) was dropwise added to the suspension under ice-cooling, followed by stirring for 2 hours. Water was added to the mixture and the resultant was extracted with ethyl acetate. The organic layer was washed with a saturated saline and and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (hexane:chloroform = 1:1) to give Compound IIb-b (74.8 g, 87.9%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.00(t, J=7.4Hz, 3H), 1.37(d, J=6.4Hz, 3H), 2.04(m, 2H), 3.32(s, 3H), 4.84-4.91(m, 1H), 4.86(s, 1H), 5.05(s, 1H), 6.90(d, J=7.4Hz, 1H), 7.02-7.05(m, 2H)
MASS(m/e): 286, 284(M^+)

(Step C) 3-Bromo-2-(2-ethyl-2-buten-1-yl)-6-methoxyphenol (Compound IIb-c)

Compound IIb-b (62.0 g) obtained in Step B was dissolved in 1-methylpyrrolidinone (68 ml) followed by stirring at 170°C for 2 hours. After being allowed to stand for cooling, a saturated saline was added to the mixture followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was distilled off to give Compound IIb-c (73.9 g) as a crude pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 0.99(t, J=7.4Hz, 3H), 1.48(d, J=6.9Hz, 3H), 2.04(q, J=7.4Hz, 2H), 3.37(s, 2H), 4.71(q, J=6.9Hz, 1H), 6.79(d, J=8.9Hz, 1H), 6.98 (d, J=8.91Hz, 1H), 8.86(brs, 1H)
MASS(m/e): 286, 284(M^+)

(Step D) 4-Bromo-2,2-diethyl-7-methoxy-2,3-dihydrobenzofuran (Compound IIb-d)

Compound IIb-c (73.9 g) obtained in Step C was dissolved in methanol (740 ml), and sulfuric acid (74 ml) was dropwise added thereto under ice-cooling, followed by heating under reflux for 3 hours. After being allowed to stand for cooling, the mixture was concentrated and water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 8:1) to give Compound IIb-d (70.9 g, 83.0% from Compound IIb-b) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 0.86(t, J=7.4Hz, 6H), 1.69(q, J=7.4Hz, 4H), 2.95(s, 2H), 3.73(s, 3H), 6.77(d, J=8.9Hz, 1H), 6.90(d, J=8.4Hz, 1H)

(Step E) 2,2-Diethyl-7-methoxy-2,3-dihydrobenzofuran-4-carbaldehyde (Compound IIb)

Under an argon atmosphere, a solution (600 ml) of Compound IIb-d (61.6 g) obtained in Step D in THF was cooled to -78°C, and then a 1.69M solution (197 ml) of n-butyl lithium in hexane was dropwise added, followed by stirring at the same temperature for 2 hours. DMF (37 ml) was added to the reaction solution and the mixture was stirred at room temperature for 2 hours. A small amount of water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/5) to give Compound IIb (43.6 g, 86.0%) as colorless crystals.

NMR(DMSO-d_6, δ, ppm): 0.85(t, J=7.4Hz, 6H), 1.70(q, J=7.4Hz, 4H), 3.26(s, 2H), 3.87(s, 3H), 7.03(d, J=8.4Hz, 1h), 7.38(d, J=8.4Hz, 1H), 9.88(s, 1H)
MASS(m/e): 234(M^+), 205

Reference Example 3

7-Methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane]-4-carbaldehyde (Compound IIc)

(Step A) 4-Bromo-2-(2-oxocyclopentyloxy)anisole (Compound IIc-a)

A mixture of 5-bromo-2-methoxyphenol (120.0 g), 2-chloro-1-cyclopentanone (100.0 g), potassium carbonate (163.3 g), and DMF (1.2 ℓ) was stirred at 70°C for 3 hours. After being allowed to stand for cooling, water was added to the mixture followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give Compound IIc-a (141.43 g, 83.9%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.78-1.99(m, 3H), 2.21-2.40(m, 3H), 3.74(s, 3H), 4.95(t, J=7.9Hz, 1H), 6.92(d, J=9.4Hz, 1H), 7.09(dd, J=2.0Hz, 9.4Hz, 1H), 7.22 (d, J=2.0Hz, 1H)
MASS(m/z): 286, 284(M^+)

(Step B) 4-Bromo-2-(2-methylenecyclopentyloxy)anisole (Compound IIc-b)

Methyltriphenylphosphonium bromide (510.3 g) was suspended in THF (2.5 ℓ), and potassium t-butoxide (153.1 g) was added thereto under ice-cooling, followed by stirring for 3 hours under ice-cooling. A solution of Compound IId-a (141.43 g) obtained in Step A in THF (1.0 ℓ) was dropwise added to the suspension under ice-cooling, followed by stirring for one hour. Water was added to the mixture followed by extraction with ether. The organic layer was washed with

a saturated saline and and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (hexane:chloroform = 1:1) to give Compound IIc-b (108.4 g, 70.7%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.66-1.98(m, 4H), 2.21-2.42(m, 2H), 3.74(s, 3H), 5.01-5.05(m, 3H), 6.92(d, J=8.6Hz, 1H), 7.08(dd, J=1.0Hz, 8.6Hz, 1H), 7.22 (d, J=1.0Hz, 1H)
MASS(m/e): 284, 282(M^+)

(Step C) 3-Bromo-2-[(2-cyclopenten-1-yl)methyl]-6-methoxyphenol (Compound IIc-c)

Compound IIc-b (108.4 g) obtained in Step B was dissolved in 1-methylpyrrolidinone (110 ml) followed by stirring at 170°C for 3 hours. After being allowed to stand for cooling, a saturated saline was added to the mixture followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was distilled off to give Compound IIc-c (129.7 g) as a crude pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.78(m, 2H), 2.19-2 .25(m, 4H), 3.43(s, 2H), 3.78(s, 3H), 5.06(t, J=2.0Hz, 1H), 6.79(d, J=8.9, 1H), 6.99(d, J=8.9Hz, 1H), 8.92(s, 1H)
MASS(m/e): 285, 283(M^+)

(Step D) 4-Bromo-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound IIc-d)

Compound IIc-c (129.7 g) obtained in Step C was dissolved in methanol (1.3 ℓ), and sulfuric acid (130 ml) was dropwise added thereto under ice-cooling, followed by heating under reflux for 3 hours. After being allowed to stand for cooling, water was added followed by extraction with ethyl acetate. The organic layer was successively washed with a saturated aqueous solution of sodium bicarbonate and a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give Compound IIc-d (102.7 g, 94.7% yield from Compound IId-b) as pale-yellow crystals.

Melting point: 45-47 °C
NMR(DMSO-d_6, δ, ppm): 1.71-1.80(m, 6H), 1.96-2.01(m, 2H), 3.16(s, 2H), 3.74(s, 3H), 6.78(d, J=8.4Hz, 1H), 6.92(d, J=8.4Hz, 1H)
MASS(m/e): 285, 283(M^+)

(Step E) (Compound IIc)

Under an argon atmosphere, a solution (700 ml) of Compound IIc-d (102.7 g) obtained in Step D in THF was cooled to -78°C, and then a 1.56M solution (360 ml) of n-butyl lithium in hexane was dropwise added thereto, followed by stirring at the same temperature for one hour. DMF (62 ml) was added to the reaction solution and the mixture was stirred at the same temperature for 2 hours. A small amount of water was added to the reaction solution and the mixture was extracted with ethyl acetate. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (chloroform) to give Compound IIc (77.4 g, 91.9%) as colorless crystals.

Melting point: 50-52 °C
NMR(DMSO-d_6, δ, ppm): 1.75-1.86(m, 6H), 1.92-2.02(m, 2H), 3.46(s, 2H), 3.86(s, 3H), 7.04(d, J=8.4Hz, 1H), 7.40(d, J=8.4Hz, 1H), 9.88(s, 1H)
MASS(m/e): 232(M^+)

Reference Example 4

7-Methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane]-4-carbaldehyde (Compound IId)

(Step A) 4-Bromo-2-(2-oxocyclohexyloxy)anisole (Compound IId-a)

A mixture of 5-bromo-2-methoxyphenol (120.0 g), 2-chloro-1-cyclohexanone (108.0 g), potassium carbonate (163.3 g), and DMF (1.2 ℓ) was stirred at 70°C for 3 hours. After being allowed to stand for cooling, water was added to the mixture followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give Compound IId-a (138.5 g, 78.3%) as pale-yellow crystals.

Melting point: 71-73 °C

NMR(DMSO-d_6, δ, ppm): 1.54-2.02(m, 5H), 2.28-2.33(m, 2H), 2.50-2.73(m, 1H), 3.75(s, 3H), 5.03(m, 1H), 6.91(d, J=8.4Hz, 1H), 6.98(d, J=2.5Hz, 1H), 7.04 (dd, J=8.4, 2.0Hz, 1H)
MASS(m/e): 300, 298(M^+), 204, 202

(Step B) 4-Bromo-2-(2-methylenecyclohexyloxy)anisole (Compound IId-b)

Methyltriphenylphosphonium bromide (476.0 g) was suspended in THF (1.3 ℓ), and potassium t-butoxide (143.0 g) was added thereto under ice-cooling, followed by stirring for 3 hours under ice-cooling. A solution of Compound IId-a (138.5 g) obtained in Step A in THF (1.0 ℓ) was dropwise added to the suspension under ice-cooling, followed by stirring at room temperature for one hour. Water was added to the mixture followed by extraction with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (hexane:chloroform = 1:1) to give Compound IId-b (133.7 g, 97.3%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.44-1.89(m, 6H), 2.06-2.11(m, 1H), 2.26-2.30(m, 1H), 3.76(s, 3H), 4.76(t, J=4.0Hz, 1H), 4.79(s, 2H), 6.90(d, J=8.4Hz, 1H), 7.05(dd, J=2.5, 8.4Hz, 1H), 7.08(d, J=2.5Hz, 1H)
MASS(m/e): 298, 296(M^+), 204, 202

(Step C) 3-Bromo-2-[(2-cyclohexen-1-yl)methyl]-6-methoxyphenol (Compound IId-c)

Compound IId-b (133.7 g) obtained in Step B was dissolved in 1-methylpyrrolidinone (160 ml) followed by stirring at 170°C for 2 hours. After being allowed to stand for cooling, a saturated saline was added to the mixture followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and the solvent was distilled off to give Compound IId-c (169.5 g) as a crude pale-yellow oily substance.

NMR(DMSO-d_6, δ•ppm): 1.44-1.59(m, 4H), 1.87-1.99(m, 4H), 3.31(s, 2H), 3.79(s, 3H), 5.05(t, J=1.5Hz, 1H), 6.78(d, J=8.9Hz, 1H), 6.98(d, J=8.9Hz, 1H), 8.85(s, 1H)
MASS(m/e): 298, 296(M^+), 217, 215

(Step D) 4-Bromo-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane] (Compound IId-d)

Compound IId-c (169.5 g) obtained in Step C was dissolved in methanol (1.4 ℓ), and sulfuric acid (170 ml) was dropwise added thereto under ice-cooling, followed by heating under reflux for 2 hours. After being allowed to stand for cooling, the mixture was concentrated, and water was added thereto, followed by extraction with ethyl acetate. The organic layer was successively washed with a saturated aqueous solution of sodium bicarbonate and a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 9:1) to give Compound IId-d (127.8 g, 95.6% from Compound IId-b) as orange-yellow crystals.

NMR(DMSO-d_6, δ, ppm): 1.43-1.50(m, 4H), 1.65-1.77(m, 6H), 2.94(s, 2H), 3.74(s, 3H), 6.78(d, J=8.4Hz, 1H), 6.92(d, J=8.4Hz, 1H)
MASS(m/e): 298, 296(M^+), 217, 215

(Step E) (Compound IId)

Under an argon atmosphere, a solution (1.0 ℓ) of Compound IId-d (100.0 g) obtained in Step D in THF was cooled to -78°C, and a 1.70M solution (307 ml) of n-butyl lithium in hexane was dropwise added thereto, followed by stirring at the same temperature for one hour. DMF (60 ml) was added to the reaction solution and the mixture was stirred at the same temperature for 2 hours. A small amount of water was added to the reaction solution followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1) to give Compound IId (78.9 g, 95.1%) as colorless crystals.

NMR(DMSO-d_6, δ, ppm): 1.30-1.61(m, 4H), 1.66-1.76(m, 6H), 3.25(s, 2H), 3.87(s, 3H), 7.04(d, J=8.4Hz, 1H), 7.39(d, J=8.4Hz, 1H), 9.87(s, 1H)
MASS(m/e): 246(M^+)

Reference Example 5

(±)-7-Methoxy-3-methyl-2,3-dihydrobenzofuran-4-carbaldehyde (Compound IIe)

(Step A) 3-Allyloxy-2-bromo-4-methoxybenzaldehyde (Compound IIe-a)

2-Bromo-3-hydroxy-4-methoxybenzaldehyde (1.68 g) was dissolved in DMF (17 ml), and sodium hydride (0.209 g) was added thereto under ice-cooling, followed by stirring for 30 minutes. Allyl bromide (0.944 ml) was added to the mixture, followed by stirring at 60°C for one hour. After being allowed to stand for cooling, water was added to the mixture and the precipitated solid was collected by filtration. The obtained crude crystals were recrystallized from isopropanol to give Compound IIe-a (1.30 g, 66%).

Melting point: 75-78 °C
NMR($CDCl_3$, δ, ppm): 3.96(s, 3H), 4.57(d, J=8.3Hz, 2H), 5.19-5.50(m, 2H), 6.02-6.27(m, 1H), 6.95(d, J=9.3Hz, 1H), 7.75(d, J=9.3Hz, 1H), 10.27(s, 1H)

(Step B) (Compound IIe)

A mixture of Compound IIe-a (0.436 g) obtained in Step A, tributyltin hydride (0.519 ml), and azobisisobutyronitrile (AIBN) (26.4 mg) was heated under reflux for 5 hours. Further, tributyltin hydride (1.3 ml) and AIBN (52 mg) were added to the mixture followed by heating under reflux one night. After being allowed to stand for cooling, ether and a 50% aqueous solution of KF were added to the mixture, followed by stirring at room temperature for 5 hours. The insoluble matters were filtered off and the filtrate was extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (toluene/ethyl acetate = 20/1) to give Compound IIe (0.184 g, 60%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 1.31(d, J=7.2Hz, 3H), 3.86-4.07(m, 1H), 3.97(s, 3H), 4.40(dd, J=8.8, 4.5Hz, 1H), 4.60-4.72(m, 1H), 6.89(d, J=9.0Hz, 1H), 7.36(d, J=9.0Hz, 1H), 9.91(s, 1H)

Reference Example 6

7-Methoxy-2-(4-pyridyl)benzofuran-4-carbaldehyde (Compound IIf)

(Step A) 7-Methoxy-2-(4-pyridyl)benzofuran (Compound IIf-a)

Ortho-vanillin (93.0 g) and 4-picolyl chloride hydrochloride (100 g) as starting materials were dissolved in DMF (1200 ml), and potassium carbonate (337 g) and potassium iodide (30 g) were added thereto, followed by heating under reflux for 24 hours while stirring. The reaction solution was filtered using celite, the solvent was distilled off under reduced pressure, and the residue was extracted with ethyl acetate. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:2) and further washed with diethyl ether to give Compound IIf-a (26.7 g, 19.4%) as pale-yellow needles.

NMR($CDCl_3$, δ, ppm): 4.04(s, 3H), 6.84(dd, J=2Hz, 7Hz, 1H), 7.1-7.2(m, 3H), 7.70(d, J=6Hz, 2H), 8.65(d, J=6Hz, 2H)
MASS(m/e): 225(M^+)

(Step B) (Compound IIf)

Under a nitrogen stream, Compound IIf-a (3.70 g) obtained in Step A was dissolved in dichloromethane (60 ml) followed by stirring at -10°C, and titanium tetrachloride (4.00 ml) dissolved in dichloromethane (10 ml) was dropwise added thereto over 5 minutes at the same temperature. Then, dichloromethyl methyl ether (1.60 ml) was added to the mixture at the same temperature, and the mixture was warmed to room temperature followed by stirring for 20 minutes. The reaction solution was poured into ice-water containing potassium hydroxide (about 10 g) followed by stirring for some time, and the mixture was filtered using celite. The filtrate was extracted with ethyl acetate, the organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:2) to give Compound IIf (2.60 g, 62.9%) as a white solid.

Melting point: 178-179 °C

NMR($CDCl_3$, δ, ppm): 4.15(s, 3H), 6.96(d, J=8Hz, 1H), 7.72(d, J=8Hz, 1H), 7.78(d, J=6Hz, 2H), 8.01(s, 1H), 8.72(d, J=6Hz, 2H), 10.06(s, 1H)

MASS(m/e): 252(M^+-1), 224

IR(KBr, cm^{-1}): 1670, 1606, 1573

Reference Example 7

7-Methoxy-2-(2-pyridyl)benzofuran-4-carbaldehyde (Compound IIg)

(Step A) 7-Methoxy-2-(2-pyridyl)benzofuran (Compound IIg-a)

Substantially the same procedure as in Step A of Reference Example 6 was repeated using ortho-vanillin (10.0 g) and using 2-picolyl chloride hydrochloride (11.0 g) instead of 4-picolyl chloride hydrochloride to give Compound IIg-a (4.23 g, 26.5%) as colorless needles.

NMR($CDCl_3$, δ, ppm): 4.03(s, 3H), 6.84(dd, J=1Hz, 8Hz, 1H), 7.18(dd, J=8Hz, 8Hz, 1H), 7.23(ddd, J=1Hz, 5Hz, 8Hz, 1H), 7.25(dd, J=1Hz, 8Hz, 1H), 7.45(s, 1H), 7.76(ddd, J=2H z, 8Hz, 8Hz, 1H), 7.98(ddd, J=1Hz, 1Hz, 8Hz, 1H), 8.65(ddd, J=1Hz, 2Hz, 5Hz, 1H)

MASS(m/e): 225(M^+)

(Step B) (Compound IIg)

Substantially the same procedure as in Step B of Reference Example 6 was repeated using Compound IIg-a (5.00 g) obtained in Step A to give Compound IIg (3.81 g, 67.8%) as a white solid.

Melting point: 143-144 °C

NMR($CDCl_3$, δ, ppm): 4.11(s, 3H), 6.92(d, J=9Hz, 1H), 7.27(dd, J=6Hz, 8Hz, 1H), 7.72(d, J=9Hz, 1H), 7.79(ddd, J=2Hz, 8Hz, 8Hz, 1H), 7.95(d, J=8Hz, 1H), 8.12(s, 1H), 8.72(dd, J=2Hz, 6Hz, 1H), 10.09(s, 1H)

MASS(m/e): 253(M^+), 252

IR(KBr • cm^{-1}): 1670, 1575, 1475, 1309

Reference Example 8

7-Methoxy-2-phenylbenzofuran-4-carbaldehyde (Compound IIh)

(Step A) 7-Methoxy-2-(4-nitrophenyl)benzofuran (Compound IIh-a)

Substantially the same procedure as in Step A of Reference Example 6 was repeated using ortho-vanillin (50.0 g) and using 4-nitrobenzyl chloride (59.0 g) instead of 4-picolyl chloride hydrochloride to give Compound IIh-a (53.0 g, 59.8%) as a yellow solid.

NMR($CDCl_3$, δ, ppm): 4.03(s, 3H), 6.89(dd, J=2Hz, 8Hz, 1H), 7.1-7.3(m, 3H), 8.00(d, J=9Hz, 2H), 8.29(d, J=9Hz, 2H)

MASS(m/e): 269(M^+), 239, 223

(Step B) 7-Methoxy-2-phenylbenzofuran (Compound IIh-b)

Compound IIh-a (26.0 g) obtained in Step A was dissolved in ethanol (400 ml)/distilled water (40 ml), and reduced iron (26.0 g) and iron (III) chloride (1.56 g) were added thereto, followed by heating under reflux for 2 hours. The reaction solution was filtered using celite, the filtrate was concentrated under reduced pressure, and the residue was extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was dissolved in tetrahydrofuran (400 ml), and sodium nitrite (10 g) and phosphinic acid (a 32-36% aqueous solution, 400 ml) were added thereto with stirring at 0°C, followed by stirring for 7 hours. The reaction solution was adjusted to alkaline by slowly adding a 1N aqueous solution of potassium hydroxide, and then the organic layer was extracted with dichloromethane. The organic layer was dried over magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 8:1) to give Compound IIh-b (16.6 g, 77.1%) as a white solid.

NMR($CDCl_3$, δ, ppm): 4.06(s, 3H), 6.81(dd, J=2Hz, 7Hz, 1H), 7.02(s, 1H), 7.15(dd, J=7Hz, 7Hz, 1H), 7.17 (t, J=7Hz, 1H), 7.36(dd, J=2Hz, 7Hz, 1H), 7.44 (dd, J=7Hz, 8Hz, 2H), 7.89(d, J=8Hz, 2H)
MASS(m/e): 224(M^+)

(Step C) (Compound IIh)

Substantially the same procedure as in Step B of Reference Example 6 was repeated using Compound IIh-b (16.0 g) obtained in Step B to give Compound IIh (6.86 g, 38.0%) as a white solid.

Melting point: 110-111 °C
NMR($CDCl_3$, δ, ppm): 4.12(s, 3H), 6.87(d, J=9Hz, 1H), 7.3-7.5(m, 3H), 7.62(d, J=9Hz, 1H), 7.78(s, 1H), 7.91(d, J=8Hz, 2H), 10.05(s, 1H)
MASS(m/e): 252(M^+), 251
IR(KBr, cm^{-1}): 1683, 1621, 1581, 1396, 1265, 1174

Reference Example 9

2-Cyano-7-methoxybenzofuran-4-carbaldehyde (Compound IIi)

A mixture of 2-cyano-7-methoxybenzofuran (4.17 g), hexamethylenetetramine (3.38 g), and trifluoroacetic acid (62 ml) was stirred at 60 to 70°C for one hour. The mixture was concentrated and the residue was purified by silica gel column chromatography (toluene/ethyl acetate = 20/1) to give Compound IIi (1.02 g, 21%) as colorless crystals.

Melting point: 170-178 °C
NMR($CDCl_3$, δ, ppm): 4.14(s, 3H), 7.10(d, J=8.1Hz, 1H), 7.82(d, J=8.1Hz, 1H), 8.21(s, 1H), 10.05(s, 1H)

Reference Example 10

3-Ethoxycarbonylmethyl-7-methoxybenzofuran-4-carbaldehyde (Compound IIj)

(Step A) 3-[(E)-3-Ethoxycarbonyl-2-propen-1-oxy]-2-iodo-4-methoxybenzaldehyde (Compound IIj-a)

Substantially the same procedure as in Step A of Reference Example 1 was repeated using 3-hydroxy-2-iodo-4-methoxybenzaldehyde (13 g) to give Compound IIj-a (18 g, 100%) as a dark brown oily substance.

NMR($CDCl_3$, δ, ppm): 1.32(t, J=7Hz, 3H), 3.95(s, 3H), 4.24(q, J=7Hz, 2H), 4.68(dd, J=2, 4Hz, 2H), 6.35 (dt, J=2, 16Hz, 1H), 7.00(d, 9Hz, 1H), 7.13(dt, J=4, 16Hz, 1H), 7.75(d, J=9Hz, 1H), 10.0(s, 1H)
MASS(m/e): 390(M^+)

(Step B) (Compound IIj)

A mixture of Compound IIj-a (18 g) obtained in Step A, THF-acetonitrile (1:1) (18 ml), triethylamine (7.8 ml), and palladium acetate (0.73 g) was heated under reflux for 3 hours. The catalyst was removed and the filtrate was concentrated. Ethyl acetate was added to the residue, and the mixture was washed with dilute hydrochloric acid and a saturated saline and dried over sodium sulfate. The solvent was distilled off and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give Compound IIj (11 g, 87%) as pale-yellow crystals.

Melting point: 45-50 °C
NMR($CDCl_3$, δ, ppm): 1.27(t, J=7Hz, 3H), 4.05(s, 2H), 4.09(s, 3H), 4.18(q, J=7Hz, 2H), 6.91(d, 9Hz, 1H), 7.70(d, J=9Hz, 1H), 9.93(s, 1H)

Reference Example 11

Methyl 2,2-diethyl-7-methoxy-2,3-dihydrobenzofuran-4-carboxylate (Compound IIk)

(Step A) Methyl 4-methoxy-3-(1-methyl-2-oxobutan-1-yloxy) benzoate (Compound IIk-a)

A mixture of methyl 3-hydroxy-4-methoxy benzoate (19.3 g), 2-bromo-3-pentanone (19.2 ml), potassium carbonate (29.3 g), and DMF (193 ml) was stirred at 90°C for 2 hours. After being allowed to stand for cooling, water was added

to the mixture followed by extraction with toluene. The organic layer was washed with a saturated saline and dried over sodium sulfate, and the solvent was distilled off. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 3:1) to give Compound IIk-a (25.8 g, 91.5%) as a colorless oily substance.

NMR($CDCl_3$, δ, ppm): 1.08(t, J=5.8Hz, 3H), 1.52(d, J=7.0Hz, 3H), 2.47-2.90(m, 2H), 3.88(s, 3H), 3.93(s, 3H), 4.71(q, J=7.0Hz, 1H), 6.92(d, J=8.6Hz, 1H), 7.47(d, J=1.0Hz, 1H), 7.74(dd, J=1.0, 8.6Hz, 1H)
MASS(m/e): 266(M^+)

(Step B) Methyl 4-methoxy-3-(1-methyl-2-methylenebutan-1-yloxy)benzoate (Compound IIk-b)

Methyltriphenylphosphonium bromide (48.5 g) was suspended in ether (485 ml), and a 1.7N solution (78.8 ml) of n-butyl lithium in hexane was dropwise added thereto under ice-cooling. The mixture was stirred at room temperature for 30 minutes and then cooled with ice again. Compound IIb-a (25.8 g) obtained in Step A was dissolved in ether (120 ml). The solution was dropwise added to the mixture, followed by stirring for 30 minutes under ice-cooling. Water was added to the mixture followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over sodium sulfate, and the solvent was distilled off. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give Compound IIk-b (20.5 g, 80%) as a colorless oily substance.

NMR($CDCl_3$, δ, ppm): 1.10(t, J=7.6Hz, 3H), 1.51(d, J=7.0Hz, 3H), 2.02-2.20(m, 2H), 3.88(s, 3H), 3.91(s, 3H), 4.81(q, J=7.0Hz, 1H), 4.90(s, 1H), 5.10(s, 1H), 6.88(d, J=8.4Hz, 1H), 7.53(d, J=1.1Hz, 1H), 7.65(dd, J=1.1, 8.4Hz, 1H)
MASS(m/e): 264(M^+)

(Step C) Methyl 3-hydroxy-4-methoxy-2-(2-ethyl-2-buten-1-yl)benzoate (Compound IIk-c)

Compound IIk-b (20.3 g) obtained in Step B was dissolved in 1-methylpiperidone (22 ml) followed by stirring at 120°C one night and then at 180°C for 2 hours. After being allowed to stand for cooling, a saturated saline was added to the mixture followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and the solvent was distilled off. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give an oily Compound IIk-c (17.0 g, 84%) as a mixture of isomers (5:1).

NMR($CDCl_3$, δ, ppm): 0.89(t, J=7.6Hz, 0.2H), 1.06(t, J=7.6Hz, 0.8H), 1.52(d, J=7.7Hz, 0.8H), 1.75(d, J=7.7Hz, 0.2H), 2.10 and 2.12(each q, J=7.6Hz, total 2H), 3.77 and 3.78(each s, total 2H), 3.81 and 3.82(each s, total 3H), 3.91 and 3.92 (each s, total 3H), 4.80(q, J=7.7Hz, 0.8Hz), 5.31(q, J=7.7Hz, 0.2H), 5.79(s, 0.8H), 5.87(s, 0.2H), 6.74 and 6.76(each d, J=8.4Hz, total 1H), 7.40 (d, J=8.4Hz, 0.2H), 7.49(d, J=8.4Hz, 0.8H)
MASS(m/e): 264(M^+)

(Step D) Methyl 2,2-diethyl-7-methoxy-2,3-dihydrobenzofuran-4-carboxylate (Compound IIk)

Compound IIk-c (16.8 g) obtained in Step C was dissolved in methanol (170 ml), and sulfuric acid (20 ml) was dropwise added thereto under ice-cooling, followed by heating under reflux one night. After being allowed to stand for cooling, the mixture was concentrated and poured into a 1N aqueous solution of sodium hydroxide under ice-cooling. The mixture was extracted with ethyl acetate, and the organic layer was washed with a saturated saline and dried over sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1 and 3:1) to give Compound IIk (12.0 g, 73%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 0.95(t, J=8.0Hz, 6H), 1.80(q, J=8.0Hz, 4H), 3.34(s, 2H), 3.88(s, 3H), 3.92(s, 3H), 6.77(d, J=8.4Hz, 1H), 7.52(d, J=8.4Hz, 1H)
MASS(m/e): 264(M^+)

Reference Example 12

Methyl 7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane]-4-carboxylate (Compound III)

(Step A) 4-Bromo-2-(2-oxocyclopentyloxy)anisole (Compound III-a)

A mixture of 5-bromo-2-methoxyphenol (6.31 g), α-chlorocyclopentanone (6.9 ml), potassium carbonate (9.57 g), and DMF (63 ml) was stirred at 90°C for 2 hours. α-Chlorocyclopentanone (14 ml) was further added to the mixture, followed by stirring at 90°C for one hour. After being allowed to stand for cooling, water was added to the mixture fol-

lowed by extraction with ether. The organic layer was washed with a 1N aqueous solution of sodium hydroxide and then with a saturated saline, and dried over sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 2:1) to give Compound III-a (11.8 g, 99%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 1.80-2.60(m, 6H), 3.89(s, 3H), 3.90(s, 3H), 4.65-4.77(m, 1H), 6.90(d, J=8.4Hz, 1H), 7.62(d, J=2.0Hz, 1H), 7.72(dd, J=8.4, 2.0Hz, 1H)
MASS(m/z): 264(M^+)

(Step B) 4-Bromo-2-(2-methylenecyclopentyloxy)anisole (Compound III-b)

Methyltriphenylphosphonium bromide (66.2 g) was suspended in THF (600 ml), and a 1M solution (185 ml) of potassium t-butoxide in THF was dropwise added thereto under ice-cooling, followed by stirring for 30 minutes under ice-cooling. Compound III-a (35.0 g) obtained in Step A was dissolved in THF (150 ml). The solution was dropwise added to the mixture under ice-cooling followed by stirring for 15 minutes. Water was added to the mixture followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over sodium sulfate. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give Compound III-b (24.5 g, 71%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 1.60-2.65(m, 6H), 3.90(s, 3H), 3.91(s, 3H), 4.95-5.05(m, 1H), 5.09-5.20(m, 2H), 6.90(d, J=8.4Hz, 1H), 7.62(d, J=2.2Hz, 1H), 7.70 (dd, J=8.4, 2.2Hz, 1H)
MASS(m/e): 262(M^+)

(Step C) 3-Bromo-2-[(2-cyclopenten-1-yl)methyl]-4-methoxyphenol (Compound III-c)

Compound III-b (29.4 g) obtained in Step B was dissolved in 1-methylpiperidinone (32 ml) followed by stirring at 140°C for 3 hours. After being allowed to stand for cooling, a saturated saline was added to the mixture followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate and the solvent was distilled off. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 7:1) to give Compound III-c (26.4 g, 90%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 1.76-1.93(m, 2H), 2.16-2.38(m, 4H), 3.82(s, 2H), 3.82(s, 3H), 3.94(s, 3H), 5.01-5.11(m, 1H), 5.78(s, 1H), 6.75(d, J=8.5Hz, 1H), 7.50(d, J=8.5Hz, 1H)
MASS(m/e): 262(M^+)

(Step D) (Compound III)

Compound III-c (0.274 g) obtained in Step C was dissolved in methanol (10 ml), and sulfuric acid (1 ml) was dropwise added thereto under ice-cooling, follwed by heating under reflux one night. After being allowed to stand for cooling, the mixture was concentrated and poured into a 1N aqueous solution of sodium hydroxide under ice-cooling. The mixture was extracted with ethyl acetate, and the organic layer was washed with a saturated saline and dried over sodium sulfate.

The solvent was distilled off, and the residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give Compound III (0.223 g, 82%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 1.66-2.25(m, 8H), 3.51(s, 2H), 3.89(s, 3H), 3.92(s, 3H), 6.78(d, J=8.7Hz, 1H), 7.53(d, J=8.7Hz, 1H)

Reference Example 13

Methyl 7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclohexane]-4-carboxylate (Compound IIm)

(Step A) Methyl 4-methoxy-3-(2-oxocyclohexyloxy)benzoate (Compound IIm-a)

A mixture of methyl 3-hydroxy-4-methoxybenzoate (2.47 g), α-chlorocyclohexanone (2.33 ml), potassium carbonate (3.76 g), and DMF (25 ml) was stirred at 90°C for 2 hours. α-Chlorocyclohexanone (2.0 ml) was further added to the mixture, followed by stirring at 90°C for one hour. After being allowed to stand for cooling, water was added to the mixture followed by extraction with ether. The organic layer was washed with a 1N aqueous solution of sodium hydroxide and then with a saturated saline, and dried over sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 2:1) to give Compound IIm-a (3.16 g, 83%) as an oily

substance.

Melting point: 66-69 °C
NMR($CDCl_3$, δ, ppm): 1.65-1.90(m, 2H), 1.96-2.14(m, 3H), 2.32-2.72(m, 3H), 3.87(s, 3H), 3.92(s, 3H), 4.69-4.82(m, 1H), 6.90(d, J=8.0Hz, 1H), 7.43(d, J=1.5Hz, 1H), 7.70(dd, J=8.0, 1.5Hz, 1H)
MASS(m/e): 278(M^+)

(Step B) Methyl 3-(2-methylenecyclohexyloxy)-4-methoxybenzoate (Compound IIm-b)

Methyltriphenylphosphonium bromide (40.4 g) was suspended in ether (400 ml), and a 1.7N solution (64.8 ml) of n-butyl lithium in hexane was dropwise added thereto under ice-cooling, followed by stirring at room temperature for 10 minutes and then cooling with ice again. Compound IIm-a (15.7 g) obtained in Step A was dissolved in ether (16 ml). The solution was dropwise added to the mixture followed by stirring at room temperature for one hour. Water was added to the mixture under ice-cooling followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give Compound IIm-b (9.15 g, 59%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 1.45-2.18(m, 7H), 2.37-2.52(m, 1H), 3.88(s, 3H), 3.91(s, 3H), 4.62-4.75(m, 1H), 4.82(s, 1H), 4.90(s, 1H), 6.90(d, J=8.2Hz, 1H), 7.55(d, J=1.3Hz, 1H), 7.67(dd, J=8.2, 1.3Hz, 1H)
MASS(m/e): 276(M^+)

(Step C) Methyl 2-[(2-cyclohexen-1-yl)methyl]-3-hydroxy-4-methoxybenzoate (Compound IIm-c)

Compound IIm-b (9.0 g) obtained in Step B was dissolved in 1-methylpiperidinone (10 ml) followed by stirring at 140°C for 3 hours and then at 150°C for 2 hours. After being allowed to stand for cooling, a saturated saline was added to the mixture followed by extraction with ethyl acetate, and the organic layer was dried over sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give Compound IIm-c (7.63 g, 85%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 1.44-1.70(m, 4H), 1.85-2.07(m, 4H), 3.70(s, 2H), 3.82(s, 3H), 3.95(s, 3H), 5.07-5.18(m, 1H), 5.79(s, 1H), 6.77(d, J=8.0Hz, 1H), 7.48(d, J=8.0Hz, 1H)
MASS(m/e): 276(M^+)

(Step D) (Compound IIm)

Compound IIm-c (7.6 g) obtained in Step C was dissolved in methanol (100 ml), and sulfuric acid (10 ml) was dropwise added thereto under ice-cooling, followed by heating under reflux one night. After being allowed to stand for cooling, the mixture was concentrated, and the residue was poured into a saturated aqueous solution of sodium bicarbonate under ice-cooling. The mixture was extracted with ethyl acetate, the organic layer was washed with a saturated saline, and the solvent was distilled off. The residue was purified by column chromatography (silica gel, hexane:ethyl acetate = 10:1) to give Compound IIm (3.42 g, 45%) as an oily substance.

Melting point: 81-83 °C
NMR($CDCl_3$, δ, ppm): 1.25-1.95(m, 10H), 3.32(s, 2H), 3.87(s, 3H), 3.92(s, 3H), 6.77(d, J=8.2Hz, 1H), 7.51(d, J=8.2Hz, 1H).
MASS(m/e): 276(M^+)

Reference Example 14

Methyl (±)-cis-6-methoxy-1,2,3,4,4a,9b-hexahydrodibenzofuran-9-carboxylate (Compound IIn)

(Step A) 2-Bromo-3-(cyclohex-2-en-1-oxy)-4-methoxybenzaldehyde (Compound IIn-a)

Diethyl azodicarboxylate (2.7 ml) was dropwise added to a mixture of 2-bromo-3-hydroxy-4-methoxybenzaldehyde (4.0 g), THF (80 ml), 2-cyclohexen-1-ol (1.2 ml), and triphenylphosphine (4.5 g) under ice-cooling, followed by stirring at room temperature for 2 hours. The mixture was poured into water followed by extraction with ether. The organic layer was washed with a 1N aqueous solution of sodium hydroxide and with a saturated saline, and dried over sodium sulfate. The solvent was distilled off, and the residue was purified by column chromatography (hexane:ethyl acetate = 10:1 and 5:1) to give Compound IIn-a (1.8 g, 47%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.50-2.25(m, 6H), 3.94(s, 3H), 4.70-4.85(m, 1H), 5.20-6.02(m, 2H), 6.96(d, J=8Hz, 1H), 7.72(d, J=8Hz, 1H), 10.3(s, 1H)
MASS(m/e): 311(M^+)

(Step B) (±)-cis-6-Methoxy-1,2,3,4,4a,9b-hexahydrodibenzofuran-9-carbaldehyde (Compound IIn-b)

Substantially the same procedure as in Step B of Reference Example 5 was repeated using Compound IIn-a (1.1 g) obtained in Step A to give Compound IIn-b (0.45 g, 56%) as colorless crystals.

NMR($CDCl_3$, δ, ppm): 0.90-1.10(m, 1H), 1.15-1.42(m, 1H), 1.46-1.84(m, 4H), 2.00-2.20(m, 1H), 2.35-2.55(m, 1H), 3.54-3.70(m, 1H), 3.97(s, 3H), 4.60-4.71(m, 1H), 6.88(d, J=8Hz, 1H), 7.35(d, J=8Hz, 1H), 9.90(s, 1H)
MASS(m/e): 232(M^+)

(Step C) (Compound IIn)

Compound IIn-b (0.42 g) obtained in Step B was dissolved in a mixed solvent of dichloromethane (5 ml) and methanol (5 ml) followed by stirring at 0°C, and potassium hydroxide (1.6 g) was added thereto. The mixture was warmed to the room temperature and stirred for 8 hours, while iodine (0.93 g) dissolved in methanol (3 ml) was slowly and dropwise added thereto. Water was added to the reaction solution followed by extraction with dichloromethane. The organic layer was dried over magnesium sulfate and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 1/5) to give Compound IIn (0.41 g, 88%) as pale-yellow crystals.

NMR($CDCl_3$, δ, ppm): 0.90-1.10(m, 1H), 1.15 -1.35(m, 1H), 1.45-1.85(m, 4H), 2.05-2.22(m, 1H), 2.35-2.45(m, 1H), 3.50-3.65(m, 1H), 3.87(s, 3H), 3.94 (s, 3H), 4.58-4.66(m, 1H), 6.77(d, J=9Hz, 1H), 7.56(d, J=9Hz, 1H)
MASS(m/e): 262(M^+)

Reference Example 15

Methyl 2-butyl-7-methoxybenzofuran-4-carboxylate (Compound IIo)

Compound IIad (1.3 g) obtained in Reference Example 30 was dissolved in methanol (16 ml), and concentrated sulfuric acid (5 ml) was dropwise added thereto under ice-cooling, followed by heating under reflux for one hour. After being allowed to stand for cooling, the solvent was distilled off, and the residue was poured into a 1N aqueous solution of sodium hydroxide. The precipitate was collected by filtration and dried to give Compound IIo (0.82 g, 56%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 0.954(t, J=8Hz, 3H), 1.30-1.56(m, 2H), 1.64-1.89(m, 2H), 2.82(t, J=8Hz, 2H), 3.94 (s, 3H), 4.06(s, 3H), 6.76(d, J=9Hz, 1H), 6.98(s, 1H), 7.91(d, J=9H z, 1H)
MASS(m/e): 262(M^+)

Reference Example 16

Methyl 7-methoxy-2-(2-methylpropyl)benzofuran-4-carboxylate (Compound IIp)

(Step A) 7-Methoxy-2-(2-methyl-1-propen-1-yl)benzofuran (Compound IIp-a)

Substantially the same procedure as in Step B of Reference Example 2 was repeated using Compound IIad-a (6.2 g) obtained in Step A of Reference Example 30, 2-propyltriphenylphosphonium iodide (20 g), and potassium tert-butoxide (5.1 g) to give Compound IIp-a (5.7 g, 81%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.96(s, 3H), 2.09(s, 3H), 4.01(s, 3H), 6.20-6.23(brs, 1H), 6.51(s, 1H), 6.75(dd, J=4, 6Hz, 1H), 7.05-7.15(m, 2H)

(Step B) 7-Methoxy-2-(2-methylpropyl)benzofuran (Compound IIp-b)

Substantially the same procedure as in Step C of Reference Example 30 was repeated using Compound IIp-a (0.4 g) obtained in Step A to give Compound IIp-b (0.8 g, 93%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 0.980(d, J=7Hz, 6H), 2.05-2.22(m, 1H), 2.65(d, J=7Hz, 2H), 4.00(s, 3H), 6.37(s, 1H), 6.68-6.80(m, 1H), 7.05-7.15(m, 2H)

(Step C) 7-Methoxy-2-(2-methylpropyl)benzofuran-4-carbaldehyde (Compound IIp-c)

Substantially the same procedure as in Step D of Reference Example 30 was repeated using Compound IIp-b (0.38 g) obtained in Step B to give Compound IIp-c (0.29 g, 66%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 0.999(d, J=8Hz, 6H), 2.05-2.23(m, 1H), 2.70(d, J=8Hz, 2H), 4.10(s, 3H), 6.84(d, J=8Hz, 1H), 7.17(s, 1H), 7.63(d, J=8Hz, 1H), 10.0(s, 1H)

(Step D) (Compound IIp)

Substantially the same procedure as in Step C of Reference Example 14 was repeated using Compound IIp-c (2.7 g) obtained in Step C to give Compound IIp (3.0 g, 100%) as pale-yellow crystals.

NMR($CDCl_3$, δ, ppm): 1.00(d, J=7Hz, 6H), 2.05-2.25(m, 1H), 2.69(d, J=7Hz, 2H), 3.94(s, 3H), 4.06(s, 3H), 6.76(d, J=8Hz, 1H), 6.99(s, 1H), 7.91(d, J=8Hz, 1H)

Reference Example 17

Methyl 7-methoxy-2-(4-pyridyl)benzofuran-4-carboxylate (Compound IIq)

Compound IIf (1.80 g) obtained in Reference Example 6 was dissolved in a mixed solvent of dichloromethane (40 ml) and methanol (80 ml) followed by stirring at 0°C, and potassium hydroxide (8.0 g) was added thereto. The mixture was warmed to the room temperature and stirred for 12 hours, while iodine (13.5 g) dissolved in methanol (30 ml) was slowly and dropwise added thereto. The reaction solution was extracted with dichloromethane, the organic layer was dried over magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 1:3) to give Compound IIq (1.50 g, 74.5%) as a white solid.

NMR($CDCl_3$, δ, ppm): 4.00(s, 3H), 4.10(s, 3H), 6.87(d, J=9Hz, 1H), 7.78(d, J=7Hz, 2H), 7.85(s, 1H), 7.99(d, J=9Hz, 1H), 8.70(d, J=7Hz, 2H)

Reference Example 18

Methyl 7-methoxy-2-(2-pyridyl)benzofuran-4-carboxylate (Compound IIr)

Substantially the same procedure as in Reference Example 17 was repeated using Compound IIg (5.50 g) obtained in Reference Example 7 to give Compound IIr (4.05 g, 65.9%) as a white solid.

Melting point: 148-149 °C
NMR($CDCl_3$, δ, ppm): 3.99(s, 3H), 4.10(s, 3H), 6.87(d, J=8Hz, 1H), 7.27(dd, J=6Hz, 8Hz, 1H), 7.78(ddd, J=2Hz, 8Hz, 8Hz, 1H), 7.95(s, 1H), 7.97(d, J=8Hz, 1H), 7.97(d, J=8Hz, 1H), 8.71(dd, J=2Hz, 6Hz, 1H)
MASS(m/e): 283(M^+), 252
IR(KBr, cm^{-1}): 1712, 1585, 1274, 1265, 1193, 1147

Reference Example 19

Methyl 7-methoxy-2-phenylbenzofuran-4-carboxylate (Compound IIs)

Substantially the same procedure as in Reference Example 17 was repeated using Compound IIh (3.00 g) obtained in Reference Example 8 to give Compound IIs (2.72 g, 85.8%) as a white solid.

Melting point: 117-118 °C NMR($CDCl_3$, δ, ppm): 3.97(s, 3H), 4.09(s, 3H), 6.81(d, J=9Hz, 1H), 7.3-7.5(m, 3H), 7.62(s, 1H), 7.93(d, J=9Hz, 1H), 7.94(d, J=9Hz.2H)
MASS(m/e): 282(M^+), 251
IR(KBr, cm^{-1}): 1701, 1620, 1292, 1220, 1095

Reference Example 20

Methyl 2-(2-ethylphenyl)-7-methoxybenzofuran-4-carboxylate (Compound IIt)

(Step A) 2-(2-Cyanophenyl)-7-methoxybenzofuran (Compound IIt-a)

Substantially the same procedure as in Step A of Reference Example 17 was repeated using ortho-vanillin (38.8 g) and using α-bromoorthotolunitrile (50.0 g) instead of 4-picolyl chloride hydrochloride to give Compound IIt-a (39.6 g, 62.3%) as colorless needles.

NMR($CDCl_3$, δ, ppm): 4.05(s, 3H), 6.87(d, J=8Hz, 1H), 7.1-7.3(m, 2H), 7.41(dd, J=7Hz, 7Hz, 1H), 7.70 (dd, J=8Hz, 8Hz, 1H), 7.74(s, 1H), 7.77(d, J=8Hz, 1H), 8.17(d, J=7Hz, 1H)

(Step B) 2-(2-Formylphenyl)-7-methoxybenzofuran (Compound IIt-b)

Compound IIt-a (26.0 g) obtained in Step A was dissolved in dry dichloromethane (500 ml), and the solution was cooled to -78°C followed by stirring. A 1.0M solution (156 ml) of diisobutylaluminium hydride in toluene was dropwise added to the mixture followed by stirring for one hour while warming the solution to the room temperature. A saturated aqueous solution of ammonium chloride was added to the reaction solution, and ethyl acetate and a 5% aqueous solution of sulfuric acid were added thereto, followed by stirring at room temperature for 30 minutes. The mixture was extracted with ethyl acetate, the organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was washed with diethyl ether to give Compound IIt-b (20.0 g, 76.0%) as a pale-yellow solid.

NMR($CDCl_3$, δ, ppm): 4.03(s, 3H), 6.86(dd, J=2Hz, 7Hz, 1H), 6.95(s, 1H), 7.2-7.3(m, 2H), 7.53(dd, J=7.5Hz, 7.5Hz, 1H), 7.67(dd, J=2Hz, 6Hz, 1H), 7.87(d, J=8Hz, 1H), 8.04(d, J=7.5Hz, 1H), 10.47 (s, 1H)

(Step C) 2-(2-Ethenylphenyl)-7-methoxybenzofuran (Compound IIt-c)

Methyltriphenylphosphonium bromide (33.1 g) was dissolved in dry tetrahydrofuran (300 ml) followed by stirring at 0°C, and potassium tert-butoxide (10.0 g) was added thereto, followed by stirring at the same temperature for 30 minutes. Compound IIt-b (9.0 g) obtained in Step B was added to the reaction solution followed by stirring at room temperature for 10 minutes. Then, distilled water was added to the mixture followed by extraction with diethyl ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give Compound IIt-c (7.71 g, 86.3%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 4.04(s, 3H), 5.36(d, J=11Hz, 1H), 5.73(d, J=17Hz, 1H), 6.83(dd, J=1Hz, 8Hz, 1H), 6.86(s, 1H), 7.1-7.25(m, 3H), 7.3-7.4(m, 2H), 7.58(m, 1H), 7.85(m, 1H)
MASS(m/e): 250 (M^+), 207, 165

(Step D) 2-(2-Ethylphenyl)-7-methoxybenzofuran (Compound IIt-d)

Compound IIt-c (7.7 g) obtained in Step C and palladium-carbon (1.9 g) were added to diethyl ether (200 ml) and the mixture was subjected to hydrogenation while stirring at room temperature. After one hour, the reaction solution was filtered with celite; and the solvent was distilled off under reduced pressure from the filtrate to give Compound IIt-d as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.30(t, J=7.5Hz, 3H), 2.93(q, J=7.5Hz, 2H), 4.03(s, 3H), 6.80(dd, J=1.5Hz, 7Hz, 1H), 6.84(s, 1H), 7.1-7.4(m, 5H), 7.75(d, J=7Hz, 1H)
MASS(m/e): 252 (M^+), 237, 194

(Step E) 2-(2-Ethylphenyl)-7-methoxybenzofuran-4-carbaldehyde (Compound IIt-e)

Substantially the same procedure as in Step B of Reference Example 6 was repeated using Compound IIt-d (7.50 g) obtained in Step D to give Compound IIt-e (5.17 g, 62.1%) as a white solid.

NMR($CDCl_3$, δ, ppm): 1.29(t, J=7.5Hz, 3H), 2.96(q, J=7.5Hz, 2H), 4.13(s, 3H), 6.91(d, J=8Hz, 1H), 7.2-7.4(m, 3H), 7.64(s, 1H), 7.69(d, J=8Hz, 1H), 7.80(d, J=7Hz, 1H), 10.07(s, 1H)

MASS(m/e): 280 (M^+), 265, 247

(Step F) (Compound IIt)

Substantially the same procedure as in Step C of Reference Example 14 was repeated using Compound IIt-d (5.00 g) obtained in Step D to give Compound IIt (4.43 g, 80.0%) as a white solid.

NMR($CDCl_3$, δ, ppm): 1.29(t, J=6.5Hz, 3H), 2.94(q, J=7.5Hz, 2H), 3.96(s, 3H), 4.08(s, 3H), 6.82(d, J=8.5Hz, 1H), 7.2-7.4(m, 3H), 7.47(s, 1H), 7.77 (d, J=7Hz, 1H), 7.96(d, J=8.5Hz, 1H)
MASS(m/e): 311 (M^+), 279

Reference Example 21

Methyl 2-[2-(2-propyl)phenyl]-7-methoxybenzofuran-4-carboxylate (Compound IIu)

(Step A) 2-(2-Acetylphenyl)-7-methoxybenzofuran (Compound IIu-a)

Compound IIt-b (18.4 g) obtained in Step B of Reference Example 20 was dissolved in dry tetrahydrofuran (500 ml), and the solution was cooled to -78°C followed by stirring. A 3.0M solution (36.4 ml) of methylmagnesium bromide in diethyl ether was dropwise added to the mixture and the reaction solution was slowly warmed to the room temperature. Distilled water was added to the mixture to cease the reaction and the solution was extracted with ethyl acetate. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give 2-[2-(1-hydroxyethyl)phenyl]-7-methoxybenzofuran (17.8 g, 91.0%) as a colorless solid. Then, the solid was dissolved in dry dichloromethane (400 ml), and pyridinium chlorochromate (PCC, 27.0 g) and molecular sieve (3Å, 30.0 g) were added thereto, followed by stirring at room temperature for one hour. Then, dichloromethane and 5% sulfuric acid were added to the reaction solution, the mixture was filtered with celite, and the filtrate was extracted with dichloromethane. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give Compound IIu-a (16.6 g, 98.4%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 2.37(s, 3H), 4.01(s, 3H), 6.82(dd, J=2Hz, 6.5Hz, 1H), 6.89(s, 1H), 7.1-7.2(m, 2H), 7.4-7.6(m, 3H), 7.78(d, J=6Hz, 1H)
MASS(m/e): 266 (M^+), 207

(Step B) 2-[2-(1-Methylethenyl)-7-methoxybenzofuran (Compound IIu-b)

Substantially the same procedure as in Step C of Reference Example 20 was repeated using Compound IIu-a (16.0 g) obtained in Step A to give Compound 21 (15.6 g, 98.0%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.98(bs, 3H), 4.02(s, 3H), 5.07 (bs, 1H), 5.22(bs, 1H), 6.78(dd, J=1.5Hz, 7Hz, 1H), 7.05(s, 1H), 7.1-7.4(m, 5H), 7.91(dd, J=1.5Hz, 5Hz, 1H)
MASS(m/e): 264(M^+)

(Step C) 2-(2-Isopropylphenyl)-7-methoxybenzofuran (Compound IIu-c)

Substantially the same procedure as in Step D of Reference Example 20 was repeated using Compound IIu-b (15.3 g) obtained in Step B to give Compound IIu-c (14.0 g, 91.1%) as a colorless oily substance.

NMR($CDCl_3$, δ, ppm): 1.26(d, J=7Hz, 6H), 3.45(sep, J=7Hz, 1H), 4.00(s, 3H), 6.77(s, 1H), 6.78(dd, J=1.5, 7.5Hz, 1H), 7.1-7.3(m, 3H), 7.3-7.5(m, 2H), 7.61(d, J=7.5Hz, 1H)
MASS(m/e): 266(M^+), 219

(Step D) 2-(2-Isopropylphenyl)-7-methoxybenzofuran-4-carbaldehyde (Compound IIu-d)

Substantially the same procedure as in Step B of Reference Example 6 was repeated using Compound IIu-c (1.00 g) obtained in Step C to give Compound IIu-d (0.67 g, 60.7%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.29(d, J=7Hz, 6H), 3.45(sep, J=7Hz, 1H), 4.12(s, 3H), 6.91(d, J=8Hz, 1H), 7.25(m, 1H),

7.35-7.5(m, 2H), 7.57(s, 1H), 7.63 (d, J=7.5Hz, 1H), 7.68(d, J=8Hz, 1H), 10.08(s, 1H)
MASS(m/e): 294(M^+), 280, 261

(Step E) (Compound IIu)

Substantially the same procedure as in Step C of Reference Example 14 was repeated using Compound IIu-d (5.40 g) obtained in Step D to give Compound IIu (5.00 g, 84.0%) as a white solid.

NMR($CDCl_3$, δ, ppm): 1.29(d, J=7Hz, 6H), 3.47(sep, J=7Hz, 1H), 3.97(s, 3H), 4.09(s, 3H), 6.83(d, J=8Hz, 1H), 7.25(m, 1H), 7.41(s, 1H), 7.4-7.5(m, 2H), 7.63(dd, J=1Hz, 8.5Hz, 1H), 7.97(d, J=8Hz, 1H)
MASS(m/e): 324(M^+), 277

Reference Example 22

Methyl 7-methoxy-3-phenylbenzofuran-4-carboxylate (Compound IIv)

Substantially the same procedure as in Reference Example 15 was repeated using Compound IIah (1.32 g) obtained in Reference Example 34 to give Compound IIv (1.26 g, 91%) as a colorless oily substance.

NMR($CDCl_3$, δ, ppm): 3.16(s, 3H), 4.07(s, 3H), 6.87(d, J=9Hz, 1H), 7.31-7.44 (m, 5H), 7.68(s, 1H), 7.81 (d, J=9Hz, 1H)
MASS(m/e): 282(M^+)

Reference Example 23

7-Methoxy-2,3-dihydrobenzofuran-4-carboxylic acid (Compound IIw)

(Step A) Methyl 7-methoxybenzofuran-4-carboxylate (Compound IIw-a)

7-Methoxybenzofuran-4-carboxylic acid (0.50 g) was dissolved in methanol (10 ml), and sulfuric acid (0.6 ml) was dropwise added thereto under ice-cooling, followed by heating under reflux for one hour. Sulfuric acid (0.2 ml) was further added to the mixture followed by heating under reflux for 30 minutes. After being allowed to stand for cooling, the solvent was distilled off, and the residue was poured into a 1N aqueous solution of sodium hydroxide. The precipitate was collected by filtration and dried to give Compound IIw-a (0.53 g, 99%) as a white solid.

Melting point: 87-89 °C
NMR($CDCl_3$, δ, ppm): 3.96(s, 3H), 4.09(s, 3H), 6.83(d, J=9Hz, 1H), 7.36(d, J=1Hz, 1H), 7.70(d, J=1Hz, 1H), 7.98(d, J=9Hz, 1H)
MASS(m/e): 206(M^+)

(Step B) Methyl 7-methoxy-2,3-dihydrobenzofuran-4-carboxylate (Compound IIw-b)

Compound IIw-a (0.84 g) obtained in Step A was dissolved in ethanol (16 ml), and 5% rhodium carbon (0.17 g) was added thereto, followed by hydrogenation at normal temperature and normal pressure for 10 hours. The catalyst was removed, and then the filtrate was concentrated to give Compound IIw-b (0.80 g, 95%) a white solid.

Melting point: 68-78 °C
NMR($CDCl_3$, δ, ppm): 3.56(t, J=9Hz, 2H), 3.89(s, 3H), 3.93(s, 3H), 4.67(t, J=9Hz, 2H), 6.77(d, J=8Hz, 1H), 7.59(d, J=8Hz, 1H)

(Step C) (Compound IIw)

A mixture of Compound IIw-b (0.76 g) obtained in Step B, ethanol (3 ml), and a 2N solution of sodium hydroxide (3 ml) was heated under reflux for 3 hours. The mixture was adjusted to pH 1 by adding dilute hydrochloric acid under ice-cooling. The precipitate was collected by filtration and dried to give Compound IIw (0.64 g, 90%) as a white solid.

Melting point: 202-207 °C
NMR($CDCl_3$, δ, ppm): 3.61(t, J=9Hz, 2H), 3.95(s, 3H), 4.70(t, J=9Hz, 2H), 6.80(d, J=8Hz, 1H), 7.65(d, J=8Hz, 1H)
MASS(m/e): 194(M^+)

Reference Example 24

(±)-7-Methoxy-3-methyl-2,3-dihydrobenzofuran-4-carboxylic acid (Compound IIx)

Compound IIe (0.184 g) obtained in Reference Example 5 was dissolved in acetone (2 ml), and an aqueous solution of potassium permanganate (0.182 g) was slowly added thereto with stirring at room temperature. The insoluble matters were filtered off, and concentrated hydrochloric acid was added to the filtrate. The precipitated solid was collected by filtration and dried to give Compound IIx (0.116 g, 58.3%) as colorless crystals.

Melting point: 194-197 °C
NMR($CDCl_3$, δ, ppm): 1.36(d, J=8.0Hz, 3H), 3.89-4.09(m, 1H), 3.96(s, 3H), 4.40(dd, J=9.3, 3.0Hz, 1H), 4.56-4.70(m, 1H), 6.82(d, J=8.9Hz, 1H), 7.69(d, J=8.9Hz, 1H)

Reference Example 25

(±)-3-Ethyl-7-methoxy-2,3-dihydrobenzofuran-4-carboxylic acid (Compound IIy)

Substantially the same procedures as in Reference Example 5 and then as in Reference Example 24 were repeated using 2-bromo-3-hydroxy-4-methoxybenzaldehyde (0.64 g) and 1-bromo-2-butene to give Compound IIy (0.37 g) as colorless crystals.

Melting point: 174-177 °C
NMR($CDCl_3$, δ, ppm): 0.92(t, J=8.1Hz, 3H), 1.51-1.89(m, 2H), 3.78-4.02(m, 1H), 3.95(s, 3H), 4.50-4.66(m, 2H), 6.82(d, J=9.0Hz, 1H), 7.70(d, J=9.0Hz, 1H)

Reference Example 26

(±)-7-Methoxy-3-(2-propyl)-2,3-dihydrobenzofuran-4-carboxylic acid (Compound IIz)

Substantially the same procedures as in Reference Example 5 and then as in Reference Example 24 were repeated using 2-bromo-3-hydroxy-4-methoxybenzaldehyde (0.21 g) and 1-bromo-3-methyl-2-butene to give Compound IIz (0.163 g) as colorless crystals.

Melting point: 179-183 °C
NMR($CDCl_3$, δ, ppm): 0.67(d, J=8.7Hz, 3H), 1.01(d, J=8.7Hz, 3H), 2.14-2.32(m, 1H), 3.82-4.01(m, 1H), 3.95(s, 3H), 4.41-4.51(m, 1H), 4.68(dd, J=9.2, 3.0Hz, 1H), 6.82(d, J=9.0Hz, 1H), 7.69(d, J=9.0Hz, 1H)

Reference Example 27

(±)-3-Ethoxycarbonylmethyl-7-methoxy-2,3-dihydrobenzofuran-4-carboxylic acid (Compound IIaa)

Substantially the same procedures as in Reference Example 5 and then as in Reference Example 24 were repeated using 2-bromo-3-hydroxy-4-methoxybenzaldehyde (2.14 g) and ethyl bromocrotonate to give Compound IIaa (2.45 g) as white crystals.

NMR($CDCl_3$, δ, ppm): 1.27(t, J=5.7Hz, 3H), 2.52(dd, J=17.2, 12.3Hz, 1H), 2.98(dd, J=17.2, 4.1Hz, 1H), 3.95(s, 3H), 4.17(q, J=5.7Hz, 2H), 4.23-4.37 (m, 1H), 4.50-4.77(m, 2H), 6.85(d, J=8.2Hz, 1H), 7.70(d, J=8.2Hz, 1H)

Reference Example 28

2-Cyano-7-methoxybenzofuran-4-carboxylic acid (Compound IIab)

A mixture of Compound IIi (0.2 g) obtained in Reference Example 9, a 80% aqueous solution (2 ml) of acetic acid, sulfamic acid (0.145 g), and a 80% aqueous solution (0.084 g) of sodium chlorite was stirred at room temperature one night. The mixture was diluted with water, and then the precipitated solid was collected by filtration and dried to give Compound IIab (0.259 g, 83%) as white crystals.

NMR(DMSO-d_6, δ, ppm): 4.05(s, 3H), 7.30(d, J=9.1Hz, 1H), 8.00(d, J=9.1Hz, 1H), 8.30(s, 1H), 12.98-13.22(br, 1H)

Reference Example 29

7-Methoxybenzofuran-4-carboxylic acid (Compound IIac)

Compound IIac was synthesized according to the method described in Org. Prep. Proced. Int., 763 (1989).

Melting point: 224-226 °C
NMR(DMSO-d_6, δ, ppm): 4.00(s, 3H), 7.02(d, J=9Hz, 1H), 7.30(d, J=3Hz, 1H), 7.88(d, J=9Hz, 1H), 8.10(d, J=3Hz, 1H), 12.7-12.8(brs, 1H)
MASS(m/e): 192(M^+)

Reference Example 30

2-Butyl-7-methoxybenzofuran-4-carboxylic acid (Compound IIad)

(Step A) 7-Methoxybenzofuran-2-carbaldehyde (Compound IIad-a)

2-Cyano-7-methoxybenzofuran (0.736 g) was dissolved in dichloromethane (10 ml), and a 1.02N DIBAL solution (5.4 ml) in toluene was added thereto at -4 to -30°C, followed by stirring for one hour. Methanol and dilute hydrochloric acid were added to the mixture, and the solvent was distilled off. The obtained residue was purified by column chromatography (hexane/ethyl acetate = 10/1) to give Compound IIad-a (0.371 g, 50%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 4.04(s, 3H), 6.92-7.03(m, 1H), 7.17-7.40(m, 2H), 7.54(s, 1H), 9.90(s, 1H)

(Step B) (E/Z)-2-(1-Buten-1-yl)-7-methoxybenzofuran (Compound IIad-b)

1-Propyltriphenylphosphonium bromide (0.907 g) was suspended in ether (10 ml), and a 1.7N solution (1.42 ml) of butyl lithium in hexane was added thereto under ice-cooling, followed by stirring for one hour. A solution of Compound IIad-a (0.319 g) dissolved in ether (3.2 ml) was dropwise added to the mixture, followed by stirring for 10 minutes. Water was added to the mixture followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 30/1) to give Compound IIad-b (0.28 g, 78%) as a colorless oily mixture of isomers (2:5).

NMR($CDCl_3$, δ, ppm): 1.11 and 1.14(each t, J=7Hz, total 3H), 2.16-2.33(m, 0.3H), 2.48-2.67(m, 0.7H), 4.01 and 4.02(each s, total 3H), 5.80(dt, J=8, 10Hz, 0.7H), 6.23-6.39(m, 1H), 6.48(s, 0.3H), 6.60(dt, J=8, 14Hz, 0.3H), 6.61(s, 0.7H), 6.70-6.83(m, 1H), 7.04-7.20(m, 2H)

(Step C) 2-Butyl-7-methoxybenzofuran (Compound IIad-c)

Compound IIad-b (0.27 g) was dissolved in methanol (5.4 ml), and 10% palladium carbon (27 mg) was added thereto, followed by hydrogenation at normal temperature and normal pressure for 3 hours. The catalyst was removed, and then the filtrate was concentrated to give Compound IIad-c (0.248 g, 91%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 0.94(t, J=8Hz, 3H), 1.30-1.51(m, 2H), 1.64-1.82(m, 2H), 2.79(t, J=7Hz, 2H), 4.00 (s, 3H), 6.38(s, 1H), 6.68-6.80(m, 1H), 7.02-7.17(m, 2H)

(Step D) 2-Butyl-4-formyl-7-methoxybenzofuran (Compound IIad-d)

Compound IIad-c (1.70 g) was dissolved in DMF (17 ml), and phosphorus oxychloride (2.3 ml) was added thereto under ice-cooling, followed by stirring at 80°C for one hour. Phosphorus oxychloride (2.3 ml) was further added to the mixture under ice-cooling, followed by stirring at 80°C for 2 hours. After being allowed to stand for cooling, the mixture was poured into ice-water followed by extraction with ether. The organic layer was washed with a saturated saline and dried over sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1) to give Compound IIad-d (1.19 g, 62%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 0.97(t, J=7Hz, 3H), 1.31-1.52(m, 2H), 1.67-1.88(m, 2H), 2.83(t, J=8Hz, 2H), 4.09 (s, 3H), 6.83(d, J=9Hz, 1H), 7.14(s, 1H), 7.61(d, J=9Hz, 1H), 10.0(s, 1H)
MASS(m/e): 232(M^+)

(Step E) (Compound IIad)

Substantially the same procedure as in Reference Example 24 was repeated using Compound IIad-d (0.500 g) to give Compound IIad (0.467 g, 88%) as a white solid.

Melting point: 114-120 °C
NMR($CDCl_3$, δ, ppm): 0.97(t, J=8Hz, 3H), 1.31-1.54(m, 2H), 1.68-1.87(m, 2H), 2.85(t, J=8Hz, 2H), 4.09 (s, 3H), 6.80(d, J=9Hz, 1H), 7.07(s, 1H), 8.00(d, J=9Hz, 1H)
MASS(m/e): 248(M^+)

Reference Example 31

7-Methoxy-2-(4-pyridyl)benzofuran-4-carboxylic acid • hydrochloride (Compound IIae)

Distilled water (350 ml) and sodium hydroxide (544 mg) were added to Compound IIq (3.50 g) obtained in Reference Example 17, followed by heating under reflux for 2 hours. The solvent was distilled off from the reaction solution under reduced pressure, and the residue was dissolved in hot ethanol (500 ml). The mixture was cooled to 0°C followed by stirring. A hydrochloric acid-ethanol solution was dropwise added to the mixture followed by stirring for 20 minutes. The precipitated crystals were collected by filtration to give Compound IIae (1.83 g, 48.2%) as a white solid.

NMR(D_2O, δ, ppm): 3.61(s, 3H), 6.44(d, J=9Hz, 1H), 7.00(s, 1H), 7.12(d, J=9Hz, 1H), 7.58(d, J=7Hz, 2H), 8.30(d, J=7Hz, 2H)

Reference Example 32

7-Methoxy-2-(2-pyridyl)benzofuran-4-carboxylic acid • hydrochloride (Compound IIaf)

Substantially the same procedure as in Reference Example 31 was repeated using Compound IIr (5.00 g) obtained in Reference Example 18 to give Compound IIaf (5.04 g, 93.3%) as a white solid.

NMR(DMSO-d_6, δ, ppm): 4.07(s, 3H), 7.14(d, J=8Hz, 1H), 7.53(dd, J=6Hz, 8Hz, 1H), 7.91(d, J=8Hz, 1H), 8.02(s, 1H), 8.05-8.15(m, 2H), 8.73(d, J=6Hz, 1H)

Reference Example 33

2-Benzyl-7-methoxybenzofuran-4-carboxylic acid (Compound IIag)

(Step A) 2-Benzoyl-7-methoxybenzofuran (Compound IIag-a)

Substantially the same procedure as in Step A of Reference Example 6 was repeated using ortho-vanillin (7.8 g) and using phenacyl chloride (9.5 g) instead of 4-picolyl chloride hydrochloride to give Compound IIag-a (13.9 g, quant.) as a pale-yellow solid.

NMR($CDCl_3$, δ, ppm): 4.01(s, 3H), 6.94(dd, J=1Hz, 8Hz, 1H), 7.29-7.21(m, 2H), 7.63-7.48(m, 4H), 8.06(dd, J=1Hz, 8Hz, 2H)
MASS(m/e): 252(M^+)

(Step B) 2-Benzyl-7-methoxybenzofuran (Compound IIag-b)

Compound IIag-a (10.00 g) obtained in Step A was suspended in diethylene glycol (100 ml), and potassium hydroxide (7.57 g) and hydrazine • monohydrate (5.77 ml) were added thereto with stirring at room temperature, followed by heating under reflux for 2 hours with stirring. The reaction solution was poured into ice-water, and the mixture was adjusted to weak acidic with dilute hydrochloric acid, followed by extraction with ether. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (hexane:ethyl acetate = 30:1) to give Compound IIag-b (7.35 g, 77.8%) as a yellow oily substance.

NMR($CDCl_3$, δ, ppm): 3.98(s, 3H), 4.12(s, 2H), 6.31(s, 1H), 6.73(dd, J=1Hz, 7Hz, 2H), 7.12-7.03(m, 2H), 7.35-7.22(m, 5H)

MASS(m/e): 238(M^+)

(Step C) 2-Benzyl-7-methoxybenzofuran-4-carbaldehyde (Compound IIag-c)

Substantially the same procedure as in Step B of Reference Example 6 was repeated using Compound IIag-b (7.35 g) obtained in Step B to give Compound IIag-c (2.70 g, 32.9%) as a white solid.

(Step D) Methyl 2-benzyl-7-methoxybenzofuran-4-carboxylate (Compound IIag-d)

Substantially the same procedure as in Reference Example 17 was repeated using Compound IIag-c (2.70 g) obtained in Step C to give Compound IIag-d (1.20 g, 39.9%) as a white solid.

(Step E) 2-Benzyl-7-methoxybenzofuran-4-carboxylic acid (Compound IIag)

Substantially the same procedure as in Reference Example 31 was repeated using Compound IIag-d (1.20 g) obtained in Step D to give Compound IIag (0.39 g, 34.1%) as a white solid.

NMR(DMSO-d_6, δ, ppm): 4.01(s, 3H), 4.20(s, 2H), 6.65 (s, 1H), 7.26(d, 1H, J=8Hz), 7.39-7.28(m, 5H), 7.53(d, 1H, J=8Hz)
MASS(m/e): 282(M^+)

Reference Example 34

7-Methoxy-3-phenylbenzofuran-4-carboxylic acid (Compound IIah)

(Step A) 4-Bromo-2-phenacyloxyanisole (Compound IIah-a)

Substantially the same procedure as in Step A of Reference Example 6 was repeated using 4-bromo-2-methoxyphenol (7.0 g) and phenacyl bromide (10.6 g) to give Compound IIah-a (9.8 g, 74%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 3.83(s, 3H), 5.33(s, 2H), 6.76(d, J=8Hz, 1H), 6.95(d, J= 2Hz, 1H), 6.76(d, J=8Hz, 1H), 7.06(dd, J=2, 8Hz, 1H), 7.45-7.63(m, 3H), 7.96-7.99(m, 2H)
MASS(m/e): 320(M^+)

(Step B) 4-Bromo-7-methoxy-3-phenylbenzofuran (Compound IIah-b)

Polyphosphoric acid (50 ml) was added to Compound IIah-a (10.8 g) obtained in Step A followed by heating at 60°C for 4 hours. After being allowed to stand for cooling, the reaction solution was poured into ice followed by extraction with ether. The organic layer was washed with a saturated saline and dried over magnesium sulfate. The solvent was distilled off and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 30:1) to give Compound IIah-b (5.9 g, 58%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 4.02(s, 3H), 6.72(d, J=9Hz, 1H), 7.32(d, J=9Hz, 1H), 7.40-7.51(m, 5H), 7.62(s, 1H)
MASS(m/e): 302(M^+)

(Step C) (Compound IIah)

Substantially thee same procedure as in Step D of Reference Example 1 was repeated using Compound IIah-b (4.0 g) obtained in Step B and using dry ice instead of DMF to give Compound IIah (1.5 g, 42%) as white crystals.

NMR($CDCl_3$, δ, ppm): 4.10(s, 3H), 6.88(d, J=9Hz, 1H), 7.31-7.35(m, 5H), 7.71(s, 1H), 7.88(d, J=9Hz, 1H)
MASS(m/e): 268(M^+)

Reference Example 35

3-Ethoxycarbonylmethyl-7-methoxybenzofuran-4-carboxylic acid (Compound IIai)

Substantially the same procedure as in Reference Example 24 was repeated using Compound IIj (4.9 g) obtained in Reference Example 10 to give Compound IIai (4.4 g, 85%) as white crystals.

Melting point: 170-177 °C
NMR($CDCl_3$, δ, ppm): 1.26(t, J=7Hz, 3H), 3.98(s, 2H), 4.08(s, 3H), 4.17(q, J=7Hz, 2H), 6.85(d, J=9Hz, 1H), 7.65(s, 1H), 8.06(d, J=9Hz, 1H)

Reference Example 36

4-Benzoyl-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound IIaj)

(Step A) 4-(1-Hydroxy-1-phenylmethyl)-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound IIaj-a)

Under an argon atmosphere, a solution of Compound IIa (4.6 g) obtained in Reference Example 1 in THF (25 ml) was cooled to -78°C, and a 1.0M solution (26 ml) of phenylmagnesium bromide in THF was slowly and dropwise added thereto, followed by stirring at 0°C for one hour. A saturated aqueous solution of ammonium chloride was added to the reaction solution followed by extraction with methylene chloride. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 50/1) to give Compound IIaj-a (4.6 g, 72.2%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.32(s, 3H), 1.34(s, 3H), 2.84 (s, 2H), 3.71(s, 3H), 6.74-6.81(m, 2H), 7.28-7.30(m, 5H)

(Step B) (Compound IIaj)

Compound IIaj-a (4.0 g) obtained in Step A was dissolved in methylene chloride (140 ml), and manganese dioxide (4.0 g) was added thereto, followed by stirring at room temperature for 5 hours. The reaction solution was filtered and the obtained filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/hexane = 1/2) to give Compound IIaj (2.0 g, 67.4%) as colorless crystals.

Melting point: 65-69 °C
NMR(DMSO-d_6, δ, ppm): 1.43(s, 6H), 3.34(s, 2H), 3.85 (s, 3H), 6.94(d, J= 8.25Hz, 1H), 7.04(d, J=8.25Hz, 1H), 7.39-7.69(m, 5H)
IR(KBr, cm^{-1}): 1637, 1608, 1576, 1506, 1446
MASS(m/z): 282(M^+)

Reference Example 37

(±)-4-Benzoyl-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound IIak)

(Step A) 4-(1-Hydroxy-1-phenylmethyl)-7-methoxy-3-methyl-2,3-dihydrobenzofuran (Compound IIak-a)

Under an argon atmosphere, a solution of Compound IIe (7.0 g) obtained in Reference Example 5 in THF (70 ml) was cooled to -78°C, and a 1.0M solution (41 ml) of phenylmagnesium bromide in THF was slowly and dropwise added thereto, followed by stirring at 0°C for one hour. A saturated aqueous solution of ammonium chloride was added to the reaction solution followed by extraction with methylene chloride. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 50/1) to give Compound IIaj-a (7.8 g, 79.4%) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.18(d, J=6.93Hz, 3H), 3.25-3.40(m, 1H), 3.72(s, 3H), 4.13(dd, J=8.75Hz, 3.30Hz, 1H), 4.39(t, J=8.58Hz, 1H), 6.80(d, J=8.58Hz, 1H), 6.87(d, J=8.58Hz, 1H), 7.20-7.31 (m, 5H)

(Step B) Compound IIaj

Compound IIaj-a (5.0 g) obtained in Step A was dissolved in methylene chloride (240 ml), and manganese dioxide (5.0 g) was added thereto, followed by stirring at room temperature for 5 hours. The reaction solution was filtered and the obtained filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/hexane = 1/2) to give Compound IIaj (4.62 g, 93.1%) as a yellowish brown oily substance.

NMR(DMSO-d_6, δ, ppm): 1.10(d, J=6.93Hz, 3H), 3.79-3.86(m, 1H), 3.86(s, 3H), 4.24(dd, J=4.29Hz, 8.91Hz, 1H), 4.62(t, J=8.91Hz, 1H), 6.96(d, J=8.25Hz, 1H), 7.02(d, J=8.25Hz, 1H), 7.52-7.57 (m, 2H), 7.64-7.71(m, 3H)

Reference Example 38

4-Benzoyl-7-methoxy-2-(4-pyridyl)benzofuran (Compound IIal)

Substantially the same procedure as in Reference Example 36 was repeated using Compound IIaf (6.0 g) obtained in Reference Example 6 to give Compound IIal (5.6 g, 75%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 4.12(s, 3H), 6.83(d, J=8Hz, 1H), 7.4-7.6(m, 4H), 7.7-7.9(m, 5H), 8.69(d, J=5.5Hz, 2H)

Reference Example 39

4-Acetyl-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound IIam)

(Step A) 4-(1-Hydroxyethyl)-7-methoxy-2,2-dimethyl-2,3-dihydrobenzofuran (Compound IIam-a)

Under an argon atmosphere, a solution of Compound IIa (21 g) obtained in Reference Example 1 in THF (100 ml) was cooled to -78°C, and a 1.0M solution (122 ml) of methylmagnesium bromide in THF was slowly and dropwise added thereto, followed by stirring at 0°C for one hour. A saturated aqueous solution of ammonium chloride was added to the reaction solution followed by extraction with methylene chloride. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 50/1) to give Compound IIam-a (24.4 g, quant.) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.26(d, J=6.3Hz, 3H), 1.39(s, 3H), 1.41(s, 3H), 3.00(s, 2H), 3.71(s, 3H), 4.60-4.64(m, 1H), 4.94(d, J=4.0Hz, 1H), 6.75(s, 2H)
MASS(m/z): 282(M^+)

(Step B) (Compound IIam)

Compound IIam-a (20.9 g) obtained in Step A was dissolved in methylene chloride (200 ml), and manganese. dioxide (31 g) was added thereto, followed by stirring at room temperature for 5 hours. The reaction solution was filtered off and the obtained filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/hexane = 1/2) to give Compound IIam (12.2 g, 59.0%) as colorless crystals.

NMR(DMSO-d_6, δ, ppm): 1.40(s, 6H), 2.49(s, 3H), 3.27 (s, 2H), 3.83(s, 3H), 6.94(d, J=8.6Hz, 1H), 7.49 (d, J=8.6Hz, 1H)
MASS(m/e): 220(M^+)

Reference Example 40

4-Acetyl-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound IIan)

(Step A) 4-(1-Hydroxyethyl)-7-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound IIan-a)

Under an argon atmosphere, a solution of Compound IIc (5.5 g) obtained in Reference Example 3 in THF (20 ml) was cooled to -78°C, and a 0.95M solution (30 ml) of methylmagnesium bromide in THF was slowly and dropwise added thereto, followed by stirring at 0°C for one hour. A saturated aqueous solution of ammonium chloride was added to the reaction solution followed by extraction with methylene chloride. The organic layer was washed with a saturated saline and dried over anhydrous magnesium sulfate, and the solvent was distilled off under reduced pressure. The residue was purified by silica gel column chromatography (chloroform/methanol = 50/1) to give Compound IIan-a (6.7 g, quant.) as a pale-yellow oily substance.

NMR(DMSO-d_6, δ, ppm): 1.25(d, J=6.6Hz, 3H), 1.71-1.86 (m, 8H), 3.17(s, 2H), 3.71(s, 3H), 4.60-4.65(m, 1H), 4.96(d, J=4.0Hz, 1H), 6.74(s, 2H)

(Step B) (Compound IIan)

Compound IIan-a (6.5 g) obtained in Step A was dissolved in methylene chloride (260 ml), and pyridinium chlorochromate (6.8 g) was added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was fil-

tered and the obtained filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1/9) to give Compound IIan (2.98 g, 52.8%) as colorless crystals.

NMR(DMSO-d_6, δ, ppm): 1.71-1.99(m, 8H), 2.49(s, 3H), 3.44(s, 2H), 3.83(s, 3H), 6.93(d, J=8.6Hz, 1H), 7.48(d, J=8.6Hz, 1H)

Reference Example 41

8-Methoxy-2,2-dimethylbenzopyran-5-carboxylic acid (Compound IIao)

(Step A) Methyl 3-(1,1-dimethyl-2-propyn-1-yloxy)-4-methoxybenzoate (Compound IIao-a)

A mixture of methyl 3-hydroxy-4-methoxybenzoate (5.41 g), 3-chloro-3-methyl-1-butyne (10 ml), cesium carbonate (19.4 g), and DMF (54 ml) was stirred at 80°C for one hour. 3-Chloro-3-methyl-1-butyne (5 ml) was further added to the mixture followed by stirring at 90°C for 3 hours. After being allowed to stand for cooling, water was added to the mixture followed by extraction with ether. The organic layer was washed with a 1N aqueous solution of sodium hydroxide and with a saturated saline and dried over sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 and 7/1) to give Compound IIao-a (2.31 g, 31%) as a brown oily substance.

NMR($CDCl_3$, δ, ppm): 1.68(s, 6H), 2.54(s, 1H), 3.87(s, 3H), 3.88(s, 3H), 6.90(d, J=8Hz, 1H), 7.79(dd, J=1, 8Hz, 1H), 8.09(d, J=1Hz, 1H)

(Step B) Methyl 8-methoxy-2,2-dimethylbenzopyran-5-carboxylate (Compound IIao-b)

Compound IIao-a (2.30 g) obtained in Step A was dissolved in diethylaniline (14 ml) followed by stirring at 160°C for 5 hours. After being allowed to stand for cooling, dilute hydrochloric acid was added to the mixture followed by extraction with ether. The organic layer was washed with a saturated saline and dried over sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10/1 and 7/1) to give Compound IIao-b (2.12 g, 92%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.48(s, 6H), 3.86(s, 3H), 3.90(s, 3H), 5.78(d, J=9Hz, 1H), 6.78(d, J=8Hz, 1H), 7.33(d, J=9Hz, 1H), 7.56(d, J=8Hz, 1H)

(Step C) (Compound IIao)

Substantially the same procedure as in Reference Example 31 was repeated using Compound IIao-b (0.38 g) obtained in Step B to give Compound IIao (0.34 g, 96%) as a white solid.

Melting point: 159-166 °C
NMR($CDCl_3$, δ, ppm): 1.50(s, 6H), 3.92(s, 3H), 5.80(d, J=9Hz, 1H), 6.80(d, J=9Hz, 1H), 7.41(d, J=9Hz, 1H), 7.69(d, J=9Hz, 1H)
MASS(m/e): 234(M^+)

Reference Example 42

8-Methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-5-carboxylic acid (Compound IIap)

(Step A) Methyl 8-methoxy-2,2-dimethyl-3,4-dihydrobenzopyran-5-carboxylate (Compound IIap-a)

Substantially the same procedure as in Step C of Reference Example 30 was repeated using Compound IIao-b (1.78 g) obtained in Step B of Reference Example 41 and 10% palladium carbon (0.36 g) to give Compound IIap-a (1.31g, 73%) as a white solid.

NMR($CDCl_3$, δ, ppm): 1.40(s, 6H), 1.70-1.87(m, 2H), 3.03-3.20(m, 2H), 3.85(s, 3H), 3.90(s, 3H), 6.73 (d, J=8Hz, 1H), 7.57(d, J=8Hz, 1H)
MASS(m/e): 250(M^+)

(Step B) (Compound IIap)

Substantially the same procedure as in Reference Example 31 was repeated using Compound IIap-a (1.27 g) obtained in Step A to give Compound IIap (1.3 g, 96%) as a white solid.

NMR($CDCl_3$, δ, ppm): 1.40(s, 6H), 1.75-1.90(m, 2H), 3.11-3.26(m, 2H), 3.91(s, 3H), 6.78(d, J=9Hz, 1H), 7.73(d, J=9Hz, 1H)
MASS(m/e): 236(M^+)

Reference Example 43

5-Carboxy-8-methoxy-spiro[benzopyran-2,1'-cyclopentane] (Compound IIaq)

(Step A) 8-Methoxy-4-oxo-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane] (Compound IIaq-a)

A mixture of methyl 2-hydroxy-3-methoxyacetophenone (16 g), cyclopentanone (33 ml), pyrrolidine (15 ml), and toluene (200 ml) was heated under reflux for 3 hours. Cyclopentanone (6 ml) was further added to the mixture followed by heating under reflux for 2 hours. After being allowed to stand for cooling, ether was added to the mixture followed by washing with dilute hydrochloric acid and with a saturated saline. The mixture was dried over sodium sulfate and the solvent was distilled off to give Compound IIaq-a (20 g, 90%) as a brown oily substance.

NMR($CDCl_3$, δ, ppm): 1.54-2.00(m, 6H), 2.02-2.26(m, 2H), 2.85(s, 2H), 3.88(s, 3H), 6.90(dd, J=9, 9Hz, 1H), 7.02(d, J=9Hz, 1H), 7.48(d, J=9Hz, 1H)
MASS(m/e): 232(M^+)

(Step B) 4-Hydroxy-8-methoxy-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane] (Compound IIaq-b)

Compound IIaq-a (39 g) obtained in Step A was dissolved in methanol (300 ml), and sodium borohydride (7.5 g) was added thereto under ice-cooling, followed by stirring at room temperature for one hour. The mixture was cooled with ice again, dilute hydrochloric acid was added thereto, and the solvent was distilled off. Water was added to the residue followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over sodium sulfate, and the solvent was distilled off. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1 and 2/1) to give Compound IIaq-b (29 g, 74%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.46-2.18(m, 9H), 2.25(dd, J= 8, 12Hz, 1H), 3.82(s, 3H), 4.78-4.92(m, 1H), 6.80 (dd, J=2, 8Hz, 1H), 6.88(dd, J=8, 9Hz, 1H), 7.07 (dd, J=2, 8Hz, 1H)
MASS(m/e): 234(M^+)

(Step C) 8-Methoxy-spiro[benzopyran-2,1'-cyclopentane] (Compound IIaq-c)

Methanesulfonyl chloride (4.9 ml) was dropwise added to a mixture of Compound IIaq-b (11 g) obtained in Step B, triethylamine (8.8 ml), and dichloromethane (114 ml) under ice-cooling, followed by stirring at room temperature for 30 minutes. DBU (9.5 ml) was added to the mixture followed by heating under reflux for 7 hours. After being allowed to stand for cooling, water was added to the mixture followed by extraction with hexane. The organic layer was washed with a saturated saline and dried over sodium sulfate, and the solvent was distilled off to give Compound IIaq-c (11 g, 99%) as a brown oily substance.

NMR($CDCl_3$, δ, ppm): 1.50-1.79(m, 4H), 1.82-2.08(m, 2H), 2.11-2.32(m, 2H), 3.84(s, 3H), 5.79(d, J=10Hz, 1H), 6.35(d, J=10Hz, 1H), 6.61(dd, J=4, 6Hz, 1H), 6.71-6.87(m, 2H)

(Step D) 8-Methoxy-spiro[benzopyran-2,1'-cyclopentane]-5-carbaldehyde (Compound IIaq-d)

Phosphorus oxychloride (18 ml) was dropwise added to a mixture of Compound IIaq-c (11 g) obtained in Step C, N-methylformanilide (24 ml), and dichloroethane (53 ml) under ice-cooling, followed by stirring at 90°C for 2 hours. After being allowed to stand for cooling, the reaction solution was poured into ice-water followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over sodium sulfate. The solvent was distilled off and the residue was purified by silica gel column chromatography (hexane/ethyl acetate = 8/1) to give Compound IIaq-d (7.8 g, 65%) as an oily mixture of isomers (1:3).

NMR($CDCl_3$, δ, ppm): 1.50-1.80(m, total 4H), 1.81-2.08 (m, total 2H), 2.10-2.32(m, total 2H), 3.90 and 3.91(each s, total 3H), 5.71(d, J=9Hz, 0.75H), 5.90(d, J=9Hz, 0.25H), 6.39(d, J=9Hz, 0.75H), 6.85(d, J=8Hz, 0.25H), 7.15(d, J=1Hz, 0.75H), 7.29(d, J=1Hz, 0.75H), 7.30(d, J=8Hz, 0.25H), 7.48(d, J=9Hz, 0.25H), 9.80(s, 0.75H), 10.0(s, 0.25H)

(Step E) 8-Methoxy-5-methoxycarbonyl-spiro[benzopyran-2,1'-cyclopentane] (Compound IIaq-e)

Compound IIaq-d (21 g) obtained in Step D was dissolved in a 5% solution (400 ml) of potassium hydroxide in methanol, and iodine (45 g) was portionwise added thereto under ice-cooling, followed by stirring at room temperature for 6 hours. The mixture was cooled again with ice, the mixture was adjusted to pH 3 by adding dilute hydrochloric acid, and the solvent was distilled off. Water was added to the mixture followed by extraction with ethyl acetate. The organic layer was washed with a saturated saline and dried over sodium sulfate, and the solvent was distilled off. The residue was purified twice by silica gel column chromatography (hexane/ethyl acetate = 10/1 and toluene/ether = 80/1) to give Compound IIaq-e (5.5 g, 23%) as a pale-yellow solid.

Melting point: 48-50 °C
NMR($CDCl_3$, δ, ppm): 1.45-2.30(m, 8H), 3.85(s, 3H), 3.86(s, 3H), 5.82(d, J=9Hz, 1H), 6.76(d, J=8Hz, 1H), 7.37(d, J=9Hz, 1H), 7.53(d, J=8Hz, 1H)
MASS(m/e): 274(M^+)

(Step F) 5-Carboxy-8-methoxy-spiro[benzopyran-2,1'-cyclopentane] (Compound IIaq)

Substantially the same procedure as in Reference Example 31 was repeated using Compound IIaq-e (1.9 g) obtained in Step E to give Compound IIaq (1.7 g, 95%) as a white solid.

Melting point: 177-189 °C
NMR($CDCl_3$, δ, ppm): 1.52-2.32(m, 8H), 3.90(s, 3H), 5.88(d, J=9Hz, 1H), 6.80(d, J=9Hz, 1H), 7.45(d, J=9Hz, 1H), 7.70(d, J=9Hz, 1H)
MASS(m/e): 260(M^+)

Reference Example 44

Methyl 8-methoxy-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane]-5-carboxylate (Compound IIar)

Substantially the same procedure as in Step A of Reference Example 42 was repeated using Compound (2.0 g) obtained in Step E of Reference Example 43 to give Compound IIar (2.0 g, 100%) as an oily substance.

NMR($CDCl_3$, δ, ppm): 1.47-2.08(m, 10H), 3.17(t, J=7Hz, 2H), 3.83(s, 3H), 3.88(s, 3H), 6.70(d, J=9Hz, 1H), 7.56(d, J=9Hz, 1H)

Reference Example 45

8-Methoxy-spiro[3,4-dihydrobenzopyran-2,1'-cyclopentane]-5-carboxylic acid (Compound IIas)

Substantially the same procedure as in Reference Example 31 was repeated using Compound IIar (2.0 g) obtained in Reference Example 44 to give Compound IIas (1.8 g, 96%) as white crystals.

Melting point: 182-189 °C
NMR($CDCl_3$, δ, ppm): 1.50-2.10(m, 10H), 3.22(t, J=6Hz, 2H), 3.90(s, 3H), 6.75(d, J=8Hz, 1H),7.70(d, J=8Hz, 1H)
MASS(m/e): 262(M^+)

Reference Example 46

Methyl 8-methoxy-spiro[3,4-dihydrobenzopyran-2,1'-cyclohexane]-5-carboxylate (Compound IIat)

(Step A) 8-Methoxy-4-oxo-spiro[3,4-dihydrobenzopyran-2,1'-cyclohexane] (Compound IIat-a)

Substantially the same procedure as in Step A of Reference Example 43 was repeated using 2-hydroxy-3-methoxyacetophenone (40 g), cyclohexanone (100 ml), and pyrrolidine (40 ml) to give Compound at-a (59 g, 100%) as a

brown oily substance.

NMR($CDCl_3$, δ, ppm): 1.20-2.10(m, 10H), 2.74(s, 2H), 3.90(s, 3H), 6.90(dd, J=8, 8Hz, 1H), 7.05(dd, J=1, 8Hz, 1H), 7.46(d, J=1, 8Hz, 1H)
MASS(m/e): 246(M^+)

(Step B) 4-Hydroxy-8-methoxy-spiro[3,4-dihydrobenzopyran-2,1'-cyclohexane] (Compound IIat-b)

Substantially the same procedure as in Step B of Reference Example 43 was repeated using Compound at-a (59 g) obtained in Step A and sodium borohydride (18 g) to give Compound (51 g, 80%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.20-2.05(m, 11H), 2.26(dd, J=6, 13Hz, 1H), 3.85(s, 3H), 4.75-4.90(m, 1H), 6.80 (dd, J=1, 8Hz, 1H), 6.88(dd, J=8, 8Hz, 1H), 7.03 (dd, J=1, 8Hz, 1H)
MASS(m/e): 248(M^+)

(Step C) 8-Methoxy-spiro[benzopyran-2,1'-cyclohexane] (Compound IIat-c)

Substantially the same procedure as in Step C of Reference Example 43 was repeated using Compound at-b (50 g) obtained in Step B, triethylamine (54 ml), methanesulfonyl chloride (33 ml), and DBU (58 ml) to give Compound at-c (46 g, 100%) as a brown oily substance.

NMR($CDCl_3$, δ, ppm): 1.20-2.08(m, 10H) ,3.85(s, 3H), 5.70(d, J=9Hz, 1H), 6.33(d, J=9Hz, 1H), 6.57-6.85(m, 3H)
MASS(m/e): 230(M^+)

(Step D) 8-Methoxy-spiro[benzopyran-2,1'-cyclohexane]-5-carbaldehyde (Compound IIat-d)

Substantially the same procedure as in Step D of Reference Example 43 was repeated using Compound at-c (46 g) obtained in Step C, N-methylformanilide (100 ml), and phosphorus oxychloride (76 ml) to give Compound at-d (36 g, 69%) as an oily mixture of isomers (1:3).

NMR($CDCl_3$, δ, ppm): 1.25-2.10(m, total 10H), 3.91 and 3.94(each s, total 3H), 5.80(d, J=9Hz, 0.75H), 5.90(d, J=9Hz, 0.25H), 6.39(d, J=9Hz, 0.75H), 6.90(d, J=8Hz, 0.25H), 7.16(d, J=1Hz, 0.75H), 7.28(d, J=1Hz, 0.75H), 7.32(d, J=8Hz, 0.25H), 7.45(d, J=9Hz, 0.25H), 9.80(s, 0.75H), 10.0(s, 0.25H)

(Step E) Methyl 8-methoxy-spiro[benzopyran-2,1'-cyclohexane]-5-carboxylate (Compound IIat-e)

Substantially the same procedure as in Step E of Reference Example 43 was repeated using Compound at-d (36 g) obtained in Step D and iodide (71 g) to give Compound at-e (4.8 g, 12%) as a pale-yellow solid.

Melting point: 70-75 °C
NMR($CDCl_3$, δ, ppm): 1.20-2.03(m, 10H), 3.85(s, 3H), 3.90(s, 3H), 5.83(d, J=9Hz, 1H), 6.77(d, J=8Hz, 1H), 7.32(d, J=9Hz, 1H), 7.55(d, J=8Hz, 1H)
MASS(m/e): 288(M^+)

(Step F) Methyl 8-methoxy-spiro[3,4-dihydrobenzopyran-2,1'-cyclohexane]-5-carboxylate (Compound IIat)

Substantially the same procedure as in Step A of Reference Example 42 was repeated using Compound at-e (2.1 g) obtained in Step E to give Compound IIat (2.1 g, 100%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.25-1.94(m, 12H), 3.10(t, 7Hz, 2H), 3.84(s, 3H), 3.89(s, 3H), 6.73(d, J=9Hz, 1H), 7.55(d, J=9Hz, 1H)

Reference Example 47

4-Methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane]-7-carbaldehyde (Compound IIau)

(Step A) 4-Bromo-3-(2-oxocyclopentyloxy)anisole (Compound IIau-a)

Substantially the same procedure as in Step A of Reference Example 3 was repeated using 2-bromo-5-methoxy-

phenol [Journal of Medicinal Chemistry, 1263, (1985)] (13.0 g) to give Compound IIau-a (15.1 g, 83%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.85-2.50(m, 6H), 3.78(s, 3H), 4.53-4.59(m, 1H), 6.45(dd, J=9, 3Hz, 1H), 6.67(d, J=3Hz, 1H), 7.39(d, J=9Hz, 1H)
MASS(m/z): 284(M^+)

(Step B) 2-Bromo-4-(2-methylenecyclopentyloxy)anisole (Compound IIau-b)

Substantially the same procedure as in Step B of Reference Example 3 was repeated using Compound IIau-a (10.5 g) obtained in Step A to give Compound IIau-b (8.2 g, 79%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.66-2.62(m, 6H), 3.77(s, 3H), 4.89-5.92(m, 1H), 5.11-5.12(m, 1H), 5.22-5.23(m, 1H), 6.40(dd, J=9, 3Hz, 1H), 6.57(d, J=3Hz, 1H), 7.40(d, J=9Hz, 1H)
MASS(m/e): 282(M^+)

(Step C) 6-Bromo-2-[(2-cyclopenten-1-yl)methyl]-3-methoxyphenol (Compound IIau-c)

Substantially the same procedure as in Step C of Reference Example 3 was repeated using Compound IIau-b (8.2 g) obtained in Step B to give Compound IIau-c (7.6 g, 93%) as a brown oily substance.

NMR($CDCl_3$, δ, ppm): 1.80-1.91(m, 2H), 2.24-2.30(m, 4H), 3.47(s, 2H), 3.78(s, 3H), 5.25(s, 1H), 5.62 (s, 1H), 6.41(d, J=9Hz, 1H), 7.27(d, J=9Hz, 1H)
MASS(m/e): 282(M^+)

(Step D) 7-Bromo-4-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane] (Compound IIau-d)

Substantially the same procedure as in Step D of Reference Example 3 was repeated using Compound IIau-c (5.7 g) obtained in Step C to give Compound IIau-d (5.5 g, 96%) as a brown oily substance.

NMR($CDCl_3$, δ, ppm): 1.65-2.20(m, 8H), 3.17(s, 2H), 3.79(s, 3H), 6.28(d, J=9Hz, 1H), 7.18(d, J=9Hz, 1H)
MASS(m/e): 282(M^+)

(Step E) 4-Methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane]-7-carbaldehyde (Compound IIau)

Substantially the same procedure as in Step E of Reference Example 3 was repeated using Compound IIau-d (5.5 g) obtained in Step D to give Compound IIau (4.3 g, 95%) as colorless crystals.

NMR($CDCl_3$, δ, ppm): 1.70-2.19(m, 8H), 3.09(s, 2H), 3.88(s, 3H), 6.47(d, J=9Hz, 1H), 7.63(d, J=9Hz, 1H), 10.08(s, 1H)
MASS(m/e): 232(M^+)

Reference Example 48

4-Methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane]-7-carboxylic acid (Compound IIav)

Substantially the same procedure as in Step E of Reference Example 47 was repeated using Compound (6.9 g) obtained in Step D of Reference Example 47 and using dry ice instead of DMF to give Compound IIav (3.5 g, 58%) as white crystals.

NMR($CDCl_3$, δ, ppm): 1.68-2.23(m, 8H), 3.17(s, 2H), 3.90(s, 3H),6.55(d, J=9Hz, 1H), 7.83(d, J=9Hz, 1H), 9.63(brs, 1H)
MASS(m/e): 248(M^+)

Reference Example 49

Methyl 4-methoxy-spiro[2,3-dihydrobenzofuran-2,1'-cyclopentane]-7-carboxylate (Compound IIaw)

Substantially the same procedure as in Reference Example 15 was repeated using Compound IIav (1.0 g) obtained

in Reference Example 48 to give Compound IIaw (0.86 g, 81%) as colorless crystals.

NMR($CDCl_3$, δ, ppm): 1.70-2.22(m, 8H), 3.06(s, 2H), 3.85(s, 3H), 3.87(s, 3H), 6.42(d, J=9Hz, 1H), 7.75(d, J=9Hz, 1H)
MASS(m/e): 262(M^+)

Reference Example 50

7-Methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane]-4-carbaldehyde (Compound IIax)

(Step A) 7-Methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane] (Compound IIax-a)

A mixture of 3-methoxycatechol (22.6 g), cyclopentanone (27.1 g), methyl orthoformate (34.2 g), p-toluenesulfonic acid • monohydrate (0.2 g), and benzene (300 ml) was heated under reflux for 24 hours. After being allowed to stand for cooling, a dilute solution of sodium hydroxide was added to the mixture followed by extraction with ether. The organic layer was washed with a saturated saline and dried over anhydrous potassium carbonate. The solvent was distilled off under reduced pressure to give Compound IIax-a (30 g, 90%) as a colorless oily substance.

NMR($CDCl_3$, δ, ppm): 1.79-1.89(m, 4H), 2.06-2.21(m, 4H), 3.89(s, 3H), 6.44-6.50(m, 2H), 6.74(t, J=8Hz, 1H)
MASS(m/e): 206(M^+)

(Step B) (Compound IIax)

Compound IIax-a (17.0 g) obtained in Step A was dissolved in dimethylformamide (100 ml), and phosphorus oxychloride (23.1 ml) was added thereto, followed by heating at 60°C for 6 hours. After being allowed to stand for cooling, the reaction solution was poured into ice followed by extraction with ether. The organic layer was washed with a saturated saline and dried over anhydrous potassium carbonate. The solvent was distilled off and the residue was purified by silica gel column chromatography (hexane:ethyl acetate = 20:1) to give Compound IIax (2.1 g, 11%) as colorless crystals.

NMR($CDCl_3$, δ, ppm): 1.83-1.91(m, 4H), 2.14-2.24(m, 4H), 3.97(s, 3H), 6.58 (d, J=9Hz, 1H), 7.27(d, J=9Hz, 1H), 9.99(s, 1H)
MASS(m/e): 234(M^+)

Reference Example 51

Methyl 7-methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane]-4-carboxylate (Compound IIay)

Substantially the same procedure as in Step C of Reference Example 14 was repeated using Compound IIay (3.7 g) obtained in Reference Example 50 to give Compound IIay (2.7 g, 64%) as a colorless oily substance.

NMR($CDCl_3$, δ, ppm): 1.84-1.90(m, 4H), 2.11-2.25(m, 4H), 3.88(s, 3H), 3.94(s, 3H), 6.52(d, J=9Hz, 1H), 7.40(d, J=9Hz, 1H)
MASS(m/e): 264(M^+)

Reference Example 52

7-Methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane]-4-carboxylic acid (Compound IIaz)

Substantially the same procedure as in Reference Example 31 was repeated using Compound IIay (1.70 g) obtained in Reference Example 51 to give Compound IIaz (1.54 g, 96%) as colorless crystals.

NMR($CDCl_3$, δ, ppm): 1.83-1.91(m, 4H), 2.14-2.24(m, 4H), 3.97(s, 3H), 6.58(d, J=9Hz, 1H), 7.27(d, J=9Hz, 1H), 9.63(brs, 1H)
MASS(m/e): 250(M^+)

Reference Example 53

7-Benzoyl-4-methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane] (Compound IIba)

(Step A) 7-(1-Hydroxy-1-phenyl)methyl-4-methoxy-spiro[1,3-benzodioxole-2,1'-cyclopentane] (Compound IIba-a)

Substantially the same procedure as in Step A of Reference Example 36 was repeated using Compound IIax (4.4 g) obtained in Reference Example 50 to give Compound IIba-a (5.6 g, 95%) as a pale-yellow oily substance.

NMR($CDCl_3$, δ, ppm): 1.77-1.87(m, 4H), 2.03-2.18(m, 4H), 2.48(d, J=4Hz, 1H), 3.85(s, 3H), 5.92(d, J=4Hz, 1H), 6.43(d, J=9Hz, 1H), 7.15(d, J=9Hz, 1H), 7.22-7.43(m, 5H)
MASS(m/e): 312(M^+)

(Step B) (Compound IIba)

Substantially the same procedure as in Step B of Reference Example 36 was repeated using Compound IIba-a (5.6 g) obtained in Step A to give Compound IIba (4.9 g, 88%) as a colorless oily substance.

NMR($CDCl_3$, δ, ppm): 1.72-1.83(m, 4H), 2.04-2.18(m, 4H), 3.94(s, 3H), 6.56(d, J=9Hz, 1H), 6.68(d, J=9Hz, 1H), 7.40-7.57(m, 3H), 7.77-7.81(m, 2H)
MASS(m/e): 310(M^+)

Preparation Example 1 Tablet

Tablets having the following composition are prepared according to a conventional method.

Compound 68	50 mg
Lactose	60 mg
Potato starch	50 mg
Polyvinyl alcohol	2 mg
Magnesium stearate	1 mg
Tar dye	a trace amount

Preparation Example 2 Powder

Powder having the following composition is prepared according to a conventional method.

Compound 68	50 mg
Lactose	250 mg

Preparation Example 3 Nasal inhalation

A nasal inhalation having the following composition is prepared according to a conventional method.

Compound 68	1 mg
Lactose	20 mg

Preparation Example 4 Ophthalmic preparation

An ophthalmic preparation having the following composition is prepared according to a conventional method.

Compound 68	10 mg
Sodium chloride	20 mg
Methylparaben	0.1 mg
Propylparaben	0.1 mg
Injectable water	q.s. 1.0 ml

Preparation Example 5 Transdermal therapeutic system

A transdermal therapeutic system having the following composition is prepared according to a conventional method.

Compound 68	10 g
White beeswax	80 g
Stearyl alcohol	30 g
Cholesterol	30 g
White vaseline	q.s. 1,000 g

Preparation Example 6 Suppository

A suppository having the following composition is prepared according to a conventional method.

Compound 68	10 mg
Witepsol W-15	1.79 g

Preparation Example 7 Injectable Preparation

An injectable preparation having the following composition is prepared according to a conventional method.

Compound 68	10 mg
Injectable water	q.s. 1.0 ml

Preparation Example 8 Syrup

A syrup having the following composition is prepared according to a conventional method.

Compound 68	10 mg
Sucrose	300 mg
Methylparaben	0.5 mg
Sodium benzoate	0.5 mg
Lemon flavor	as necessary
Dye	as necessary
Purified water	q.s. 1.0 ml

Preparation Example 9 Nasal spray

A nasal spray having the following composition is prepared according to a conventional method.

Compound 68	10 mg
Sodium chloride	8 mg
Benzalkonium chloride	0.1 mg
Carbopol	10 mg
Purified water	q.s. 1.0 ml

Preparation Example 10 Tablet

Tablets having the following composition are prepared according to a conventional method.

Compound 68	10 mg
Lactose	140 mg
Corn starch	45 mg
Sodium croscarmellose	10 mg
Hydroxypropyl cellulose L	4 mg
Magnesium stearate	1 mg

Preparation Example 11 Capsule

Capsules having the following composition are prepared according to a conventional method.

Compound 68	10 mg
Lactose	185 mg
Sodium croscarmellose	10 mg
Hydroxypropyl cellulose L	4 mg
Magnesium stearate	1 mg

Preparation Example 12 Dry syrup

A dry syrup having the following composition is prepared according to a conventional method.

Compound 68	10 mg
Sucrose	0.7 g
D-mannitol	0.28 g
Pullulan	20 mg

Preparation Example 13 Granules

Granules having the following composition are prepared according to a conventional method.

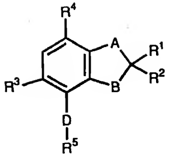
Compound 68	10 mg
Lactose	0.8 g
Corn starch	0.17 g
Hydroxypropyl cellulose L	30 mg

<u>Industrial Applicability</u>

The present invention can provide oxygen-containing heterocyclic compounds which exhibit PDE IV inhibitory activity and which are useful as therapeutic agents for asthma, allergy, rheumatoid arthritis, psoriasis, myocardial infarction, depression, amnesia, multiple sclerosis, Crohn's disease, systemic lupus erythematosus, diabetes, wounds, AIDS, and the like.

Claims

1. An oxygen-containing heterocyclic compound represented by following Formula (I):



(I)

wherein R^1 and R^2 independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, aralkyl, cyano, or $-(CH_2)_n-E^1-CO-G^1$ {wherein E^1 represents a bond, O, or NH; and G^1 represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, aralkyl, OR^6 (wherein R^6 represents hydrogen, lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or aralkyl), or NR^7R^8 (wherein R^7 and R^8 independently represent hydrogen, lower alkyl, cycloalkyl, polycycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, substituted or unsubstituted aralkyl, or heteroarylalkyl; or R^7 and R^8 are combined to represent a substituted or unsubstituted heterocyclic group containing a nitrogen atom); and n represents an integer of 0 to 4);

R^1 and R^2 are combined to represent a saturated carbon ring together with a carbon atom adjacent thereto; or R^2, and
R^{11} or R^{13} described below are combined to form a single bond;
R^3 represents hydrogen, phenyl, or halogen;
R^4 represents hydroxy or substituted or unsubstituted lower alkoxy;
A represents $-C(R^9)(R^{10})-$ (wherein R^9 and R^{10} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, or polycycloalkyl) or O;
B represents O, NR^{11} {wherein R^{11} represents hydrogen, lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, aralkyl, or $-(CH_2)_m-E^2-CO-G^2$ (wherein E^2, G^2, and m have the same meanings as the above-described E^1, G^1, and n, respectively); or R^{11} and R^2 are combined to form a single bond}, $-C(R^{12})(R^{13})-$ {wherein R^{12} and R^{13} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, aralkyl, cyano, or $-(CH_2)_p-E^3-CO-G^3$ (wherein E^3, G^3, and p have the same meanings as the above-described E^1, G^1, and n, respectively); R^{13} and R^2 are combined to form a single bond; or R^{13} and R^2 are combined to form a saturated carbon ring together with two carbon atoms adjacent thereto}; or $-C(R^{14})(R^{15})-C(R^{16})(R^{17})-$ {wherein R^{14} and R^{15} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, aralkyl, substituted or unsubstituted aryl, or a substituted or unsubstituted aromatic heterocyclic group; or R^{14} and R^{15} are combined to form O; and R^{16} and R^{17} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, aralkyl, substituted or unsubstituted aryl, or a substituted or unsubstituted aromatic heterocyclic group; or R^{17} and R^{15} are combined to form a single bond; or R^{17} and R^{15} are combined to form a saturated carbon ring together with two carbon atoms adjacent thereto};
D represents (i) $-C(R^{18})(R^{19})-X-$ {wherein R^{18} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, hydroxy, substituted or unsubstituted lower alkoxy, or lower alkanoyloxy; and R^{19} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, hydroxy, substituted or unsubstituted lower alkoxy, lower alkanoyloxy, lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, or cyano; or R^{18} and R^{19} are combined to form O, S, or NR^{20} (wherein R^{20} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, hydroxy, substituted or unsubstituted lower alkoxy, or lower alkanoyloxy); X represents $-C(R^{21})(R^{22})-$ (wherein R^{21} and R^{22} independently represent hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group,

lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, or cyano) or S; or X represents NR^{23} (wherein R^{23} represents hydrogen, lower alkyl, cycloalkyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, or aralkyl) unless R^1 and R^2 simultaneously represent substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, or cycloalkenyl in the above definition), (ii) $-C(R^{19a})=Y-$ {wherein R^{19a} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, hydroxy, substituted or unsubstituted lower alkoxy, lower alkanoyloxy, lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, or cyano; and Y represents $-C(R^{24})-Z-$(wherein R^{24} represents hydrogen, substituted or unsubstituted lower alkyl, cycloalkyl, polycycloalkyl, lower alkenyl, cycloalkenyl, substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, lower alkanoyl, cycloalkanoyl, lower alkoxycarbonyl, or cyano; or R^{24} and R^{19a} are combined to form a single bond; and Z represents CONH, $CONHCH_2$, or a bond) or N}, or (iii) a bond; and R^5 represents substituted or unsubstituted aryl, a substituted or unsubstituted aromatic heterocyclic group, cycloalkyl, pyridine-N-oxide, cyano, or lower alkoxycarbonyl; or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/01327

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl6 C07D307/80, 307/94, 405/06, 405/10, 405/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int. Cl6 C07D307/80, 307/94, 405/06, 405/10, 405/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	JP, 1-110684, A (Eli Lilly and Co.), April 27, 1989 (27. 04. 89), Full descriptions & EP, 307172, A2 & AU, 8821916, A & DK, 8804944, A & PT, 88438, A & CN, 1031841, A & ZA, 8806585, A & IL, 87674, A & AU, 9169953, A & SU, 1777602, A3	1
X	JP, 1-207267, A (Yamanouchi Pharmaceutical Co., Ltd.), August 21, 1989 (21. 08. 89), Full desctiptions & EP, 285267, A2 & AU, 8812751, A & NO, 8800992, A & FI, 8800990, A	1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed
- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
August 5, 1996 (05. 08. 96)	August 13, 1996 (13. 08. 96)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

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International application No.
PCT/JP96/01327

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X	FR, 2507604, A2 (Delalande S. A.), December 17, 1982 (17. 12. 82), Full descriptions (Family: none)	1
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/01327

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP96/01327

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	J. Chem. Soc., Perkin Trans. 1,(7), (1982), p. 1455-66, Crombie, Leslie et al., "Natural products of Thailand high. delta, 1-THC-strain Cannabis. The bibenzyl-spiran-dihydrophenanthrere group: rerations with cannabinoids and canniflavones"	1
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X	Tetrahedron Lett., (32), (1975), p. 2795-8, Cannon, J. R. et al., "Structures of nine quinones isolated from two Conospermum species"	1
X	J. Org. Chem., 60(1), (1995), p. 84-8, Crich, David et al., "Inhibition of Rearrangements in Stannane-Mediated Radical Reduction Reactions by Catalytic Quantities of Diphenyl Deslenide. An Example of Polarity Reversal Catalysis"	1

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